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STUDIES OF MALE SURVIVORS OF MYOCARDIAL INFARCTION DUE TO "ESSENTIAL" ATHEROSCLEROSIS*

I. CHARACTERISTICS OF THE PATIENTS

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WESTERN CIVILIZATION in this twentieth century has witnessed a phenomenon unique in medical history: the precipitate rise of atherosclerotic coronary heart disease (C.H.D.) from obscurity to the leading cause of death. In recent years, this one disease alone accounted for one-quarter of all deaths in the Department of Veterans Affairs hospitals in Canada.[1] Accordingly, the Department, in 1952, initiated a country-wide, long-term study of the etiology, pathogenesis and clinical course of this condition.

The project at Toronto, designed as a comprehensive investigation of patients with C.H.D., examined multiple aspects of this problem, including the family history of affected patients, their personal habits and environment, diet, body build, clinical findings, radiographic features, biochemical findings (serum lipids, lipoproteins, uric acid, clearing factor activity), thyroid function, blood coagulation characteristics, prognosis and pathology. The subjects are being followed up for a 10-year period in an effort to gauge the degree of progression of their clinical coronary disease and to correlate it with the results of the initial and repeat examinations, especially of the serum lipids and lipoproteins. The information obtained will be published in a series of detailed papers. Several interim abstracts have already appeared.[2-7]

This first paper in this series is concerned with a general characterization of the coronary patients. It was considered that neither the increase in, nor the striking geographical disparity of, the prevalence of C.H.D. could be explained by such factors as sex and familial predisposition. Therefore, certain variable constitutional, personal and environmental factors considered to be relevant to the presence or absence of C.H.D. were assessed. These included race, family history, marital status and number of children, occupation, activity, athletic activity, past health, use of tobacco and alcohol, body habitus (height, chest circumference and weight), apparent ageing and psychological type.

Scrutiny of the many contributions of previous authors showed that, although these factors have been studied repeatedly, their actual significance in C.H.D. remains ill-defined. Controls have been badly selected or completely lacking; clinical impression has too often been accepted uncritically in place of quantitative evaluation; statistical techniques have often been poor or frankly fallacious, as, for example, in the improper use of ratios (*vide infra*).

In contrast to most previous studies, this project has been designed to examine "essential" atherosclerosis, that is, atherosclerosis unaccompanied by any condition known or believed to be a causative or aggravating factor, such as hypertension, diabetes, hypothyroidism, nephrosis or gout. In this way it was hoped that a more clear-cut picture of the characteristics of the coronary patient, his biochemical make-up and the course of his disease could be obtained.

The term "primary" could be used to describe this type of atherosclerosis, designating as it does a condition not secondary to any known cause or organic disease. The designation "essential" atherosclerosis was employed in analogy to "essential hypertension". This, too, could be called a "negative concept" (Fishberg), a diagnosis of exclusion and therefore to some extent dependent not only upon the tools at the disposal of the examiner but on his clinical acumen as well. It may be that "essential atherosclerosis" results from one major determining cause or it may represent the consequences of a multitude of interacting factors, no one of which is, in itself, capable of producing the disease. For example, C.H.D. in persons of middle age is likely multifactorial in etiology, whereas in the young it may have only one major cause, such as familial hypercholesterolemia.

In essence, this paper, by determining the characteristics of coronary patients, will attempt to answer Osler's classical question, "What kind of patient does the disease have?"

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Selection of Clinical Material

A preliminary survey disclosed many differences and even contradictions among the findings of previous investigators, most of which could be attributed to disparities in the composition of their clinical material, both coronary and control. These disagreements appeared to be due not only to differences in the source of the material, but to the varying and often ill-defined criteria used for selection. The requirements for inclusion in this study were strictly established. The coronary group had unequivocal evidence, anamnestic and electrocardiographic, of ischemic heart disease as manifested by myocardial infarction. Patients with valvular disease, syphilis, anemia or polycythemia, thromboangiitis obliterans or polyarteritis nodosa, were excluded, so that the cause for the ischemia was almost certainly atherosclerosis in every case included. The coronary subjects were selected by review of about 5000 hospital files classified under "arteriosclerotic heart disease" and "myocardial infarction". Controls of the same hospital population were taken at random from files classified under such minor diseases as "hemorrhoids" and "respiratory infection", thought not to affect the variates to be studied. Thus, any dissimilarities that could be demonstrated between the two groups should be real, and related to the absence or presence of clinical C.H.D.

Both groups were chosen from patients free of hypertension, arbitrarily defined as the persistent elevation of the blood pressure above 150/90 mm. Hg. The availability of military and medical documents afforded the unique opportunity to recognize and exclude those coronary patients with normal blood pressure levels who had had hypertension preceding their infarction. The mean blood pressures were similar in the two groups. All subjects were also free of diabetes, nephrosis and hypothyroidism, diseases commonly associated with secondary hypercholesterolemia. The presence of xanthomatosis in a patient or in his relatives was not cause for exclusion. Nor was any attempt made to exclude essential (familial) hypercholesterolemia or primary (familial) hyperlipemia, for which satisfactory criteria are, as yet, not established.

The presence of any major diseases, especially those with important metabolic consequences (hepatobiliary disease, endocrinopathies, gout, cancer or other wasting disease), was reason for exclusion from both groups. Any person in either group receiving special diets or treatment with hormones or anticoagulants was eliminated from the study. All the subjects had been discharged from hospital at least three months previous to entry in the study and were ambulatory.

Because this was a military veteran population, and because of the relative immunity of the female to coronary atherosclerosis, the number of women who could be included was so small that it was decided to restrict the study to patients of the male sex. Because of the infrequency of persons fulfilling these highly selective criteria in the extremes of life, the study was of necessity confined to subjects between 30 and 70 years, inclusive.

To allow for a reasonably satisfactory statistical evaluation, some 25 men in each decade, for each of the two groups, were assembled. The coronary group was selected first and a control group was then matched thereto, so that the mean age in each decade was similar.

The rate of refusal to participate was less than 10% and was similar in the two groups, so that no significant bias was introduced from this source.

It is of interest that only a small fraction of the clinical coronary population could meet the rigorous requirements of this project. About 20% of the subjects called upon to serve as controls on the basis of data recorded in their documents had to be disqualified after their initial physical and laboratory examinations.

Procedure

After an overnight fast, each participant, coronary and control, was investigated by the authors. This investigation included basal metabolism tests; fasting blood specimen for determination of lipids and lipoproteins; detailed family, medical and dietary history; complete physical examination; fluoroscopic and orthodiagraphic examinations; 12-lead electrocardiogram; posteroanterior and left lateral chest radiographs, and lateral radiographs of the abdomen for the detection of aortic calcification. A urinalysis, hemogram, determination of blood sugar and non-protein nitrogen levels and a Wassermann reaction were also performed on each subject. Where indicated, determinations of serum protein-bound iodine, radioactive iodine uptake, glucose tolerance test, liver function tests and fasting electrocardiographs were performed.

Composition of the Group

All the participants were males. The numbers and ages of the patients in the two groups are shown in Table I. There are approximately 25 patients in each decade and the mean ages are similar.

It is emphasized that this coronary group, by arbitrary selection (Canadian, male, military veterans, survivors of previous myocardial infarction, with no aggravating disease and no associated

TABLE I.—COMPOSITION OF THE GROUPS: NUMBER AND AGE

	Control			*Coronary*		
Decade	*n*	*Mean age*	*s*	*n*	*Mean age*	*s*
4th.....	25	34.4	2.9	25	36.3	2.8
5th.....	25	43.6	2.7	26	44.5	3.0
6th.....	27	56.0	2.4	28	55.5	2.4
7th.....	23	64.1	2.8	23	64.3	2.7
	100			102		

n = number; s = standard deviation.

disease), is far from representative of the coronary population as a whole. Moreover, the choosing of an equal number of patients in each decade (to facilitate stratified comparisons) greatly alters the age factor from that seen in an unweighted series. For example, in Cassidy's series of 1000 coronary patients, those in the fourth and fifth decade comprised only 3.2 and 14.6% respectively, of the total number.[8] It is clear then that the results of the appraisal of this coronary group cannot be applied without reservation to the general coronary population.

COMPARISONS BETWEEN THE CONTROL AND CORONARY SUBJECTS

"Racial" Factor

Investigations of racial predisposition to C.H.D. have been complicated by the lack of a satisfactory definition of "race" and by the inevitable presence of major differences other than "race" in the populations compared. In a recent appraisal, Plotz[9] concluded that in most instances the so-called "ethnic" (and geographic) differences in heart disease are, in actuality, a reflection of economic, cultural and dietary differences. This conclusion is supported by recent evidence showing that, after emigration to Western countries from their native lands, Yemenite Jews, Italians and Japanese incur an increased incidence of C.H.D.[10]

In this study, the places of birth of the subject and his parents were noted. The results of this inquiry are summarized in Table II.

TABLE II.—RACIAL ORIGIN

Birthplace	*Control* ($n = 100$)	*Coronary* ($n = 102$)
A. Of subject*		
Canada	60	65
British Isles	34	34
Other	6	3
B Of subject's parents†		
Canada	27	32
British Isles	64	65
Other	9	5

*χ^2 (Canadians vs. other) = 0.160, $p < 0.75$
†$\chi^2 = 1.555$, $p < 0.5$.

The origin of the two groups was very similar. As might be expected from the source of the subjects, the majority came from the British Isles. There was only one Jew in each group (in contrast to other studies[11, 12] in which Jews constituted a large proportion of the coronary group). There were no Negroes.

There was no significant difference in the places of birth of the parents of the subjects in the two groups. Nor was there any difference in the number of generations for which their families had been established in Canada.

The nationality or "racial extraction" of both groups, then, is similar and further testifies to the comparability of the two groups selected. There is little evidence to be obtained from this study relative to the significance of "race" in patients with C.H.D.

Familial Factor

For some three decades,[13] clinicians have acknowledged a familial tendency to C.H.D. A considerable body of evidence now supports this clinical impression.[14] However, it is among the relatives of coronary patients under the age of 40 years only that the increased prevalence of coronary disease is substantial.[11, 13]

Although many explanations have been advanced, the mechanisms of the familial occurrence of coronary disease have remained ill-defined. It has been suggested that the familial factor may not be genetic but may be only a reflection of common environmental conditions, such as similar habits of occupation, diet or psychological reaction. Or it may be that the familial tendency reflects only the co-existence of diseases such as hypertension and diabetes which commonly accompany C.H.D. and which are believed to be genetically influenced.

On the other hand, C.H.D. may be a truly genetic disorder. This is suggested by its association with body build[11] (also, *vide infra*), itself generally accepted to be genetically determined. Several possible pathways through which the genes may express themselves have been postulated. Since Osler's time, familial "faulty tubing", that is, some physicochemical defect of the coronary intima, has been assumed. Intimal thickenings of the coronary arteries in males at birth have been demonstrated by Dock,[15] who suggested that this characteristic might be inherited. Previously, Schlesinger[16] had described three main forms of anatomic coronary patterns and had suggested that the inherited occurrence of the less favourable type, left coronary artery predominating, might be responsible for the familial distribution of C.H.D. More recently, Laurie and Woods[17] have proposed that familial C.H.D. could more appropriately be attributed to the lack of an inherited (normal) coronary anastomotic supply. Glass[18] has speculated that there may be a hereditary receptivity factor or reaction factor of the tissues to circulating lipid.

There is substantial evidence that lipid metabolism is important in atherogenesis. Serum lipid levels and patterns are apparently inherited as a graded characteristic in the general population.[14] The association between elevated serum lipids and an increased incidence of C.H.D. is most clearly illustrated in patients with "familial (idiopathic) hypercholesterolemia". In this disorder, the abnormal lipid metabolism is surely the factor determining the inheritance of coronary atherosclerosis. A similar disordered metabolism, operating to a lesser degree, may explain the familial aggregation of C.H.D. in the general population.[19]

Still more recently, a decrease in clearing factor activity has been shown in subjects with a family history of C.H.D.[5] Finally, the response of the blood-clotting system to dietary fat has been found to be overactive in some individuals with a positive coronary family history.[20] This may indicate the importance of a thrombosing tendency in patients with familial coronary disease.

Some of these possibilities will be explored in this and subsequent reports. It is, of course, probable that environment and heredity will interplay and that the family occurrence of coronary heart disease may be due to different mechanisms in different families.

TABLE IV.—PREVALENCE OF CORONARY HEART DISEASE IN SIBLINGS

Decade	*4th*		*5th*		*6th*		*7th*		*Total*	
	B	*S*	*B*	*S*	*B*	*S*	*B*	*S*	*B*	*S*
CONTROL (n = 100)	0	0	0	0	1	0	1	1	2	1
	44	49	41	31	54	41	25	26	164	147
CORONARY (n = 102)	1	0	6	2	10	1	8	3	25	6
	27	35	54	53	57	55	67	56	205	199

B = Brother; *S* = Sister.
The lower figure in each case is the number of siblings about whom reliable information was obtained.
Total *B*: $\chi^2 = 14.60$, $p < 0.001$.***
Total *S*: $p = 0.126$ (Fisher's method of exact probability).

Table IV demonstrates a significantly increased number of cases of C.H.D. in the brothers of the coronary patients in all decades. This finding is in keeping with observations in previous reports.[14] The increased incidence among sisters did not reach statistical significance. Although the numbers of individuals are few, and the wastage gross and unequal, the percentage of C.H.D. in the grandparents (Table V) is somewhat higher in the coronary group than in the control group.

TABLE III.—PREVALENCE OF CORONARY HEART DISEASE IN PARENTS

Decade	*4th*			*5th*			*6th*			*7th*			*Total*		
Subjects	*F*	*M*	*P*	*F*	*M*	*P*	*F*	*M*	*P*	*F*	*M*	*P*	*F*	*M*	*P*
Control (n = 100)	7	1	1	5	2	0	3	6	1	5	3	2	20	12	4
	24	21	21	20	21	20	23	24	25	14	14	14	81	80	81
Coronary (n = 102)	12	4	3	11	8	3	6	4	1	2	3	1	31	19	8
	23	22	22	24	23	23	23	24	25	17	15	21	87	84	91

F = Father; M = Mother; P = Both parents.
The lower figure in each case is the number of parents about whom reliable information was obtained.

In the present study, a detailed family history was obtained by direct questioning of each subject. The medical condition of the parents, grandparents, siblings, aunts and uncles was noted, with particular reference to the presence of C.H.D. (and its age of onset), diabetes and hypertension. No further study of the family was undertaken. In instances in which information concerning the family was of doubtful validity, no record was made thereof.

Table III shows the prevalence of C.H.D. in the parents of coronary and control subjects. Comparison of the number of subjects who could contribute reliable information about their parents with the total number of subjects (Table I) shows that the "wastage" was small, and was about the same in the control and coronary groups. It is seen that coronary disease is more prevalent in the parents of the coronary than in the parents of the non-coronary subjects in the fourth and fifth decade. This difference, however, did not reach statistical significance. Also, it is only in these decades that a positive history is obtained more often than not. More fathers were affected than mothers. A history of coronary disease in both parents was unusual among coronary patients and occurred mainly in the parents of the younger subjects; it was even more rare in the controls, among whom it tended to occur in the older subjects.

It may be added that the average age of onset of the coronary disease of the parents was similar in the coronary and non-coronary subjects.

TABLE V.—PREVALENCE OF CORONARY HEART DISEASE IN GRANDPARENTS

Decade	*4th*	*5th*	*6th*	*7th*	*Total*
Control (n = 100)	2	1	0	0	3
	32	5	5	13	55
Coronary (n = 102)	7	11	2	0	20
	39	30	32	14	115

The lower figure in each case is the number of grandparents about whom reliable information was obtained.
Total: $\chi^2 = 3.569$, $p < 0.1$.

Data on the aunts and uncles of the subjects were too unreliable to warrant analysis.

Age of Onset of Clinical C.H.D.

Both experienced clinicians and vital statisticians agree that young people (under the age of 40 years) are now affected by C.H.D. much more often than formerly.[21] To pursue this lead, the age of onset of clinical coronary heart disease in affected fathers and grandfathers was ascertained.

Table VI demonstrates that not one of the coronary patients with a positive family history incurred his disease at a later decade than his father;

TABLE VI.—DECADE OF ONSET OF C.H.D. IN FATHERS OF CORONARY PATIENTS

Coronary Patients							
Age of onset	*Number*	*4th*	*5th*	*6th*	*7th*	*8th*	*9th*
4th	12	1	2	3	3	3	0
5th	11	0	1	2	5	3	0
6th	6	0	0	2	1	2	1
7th	2	0	0	0	1	1	0

the usual pattern was that of occurrence of the disease some two decades earlier in the subject than in his parent. It was further found that the grandparents who had suffered C.H.D. had done so later still, that is, in their seventh, eighth or ninth decades.

It is thus evident that clinical C.H.D. is being encountered in this generation at an earlier age than in former generations. Although there are several alternative explanations for this observation, such as diagnostic bias or increasing diagnostic acumen, these findings might be interpreted as displaying the phenomenon of "anticipation", that is, the development of a disease at an earlier age in each successive generation, a phenomenon which is believed to occur in such conditions as diabetes.[22] There seems to be evidence, then, that C.H.D. is not only occurring with ever-increasing frequency, but is attacking patients at a progressively earlier age. This trend, if real, is ominous.

Conclusions Regarding Familial Influences and Age of Onset

These findings confirm the many previous observations that C.H.D. is often familial, especially in patients under 50 years of age. Nevertheless, a positive family history, *per se*, does not appear to be the only factor, or even the most important one. Even involvement of both parents does not necessarily mean that the offspring will suffer this disease, nor does a negative family history necessarily imply immunity in any individual.

Because of obvious shortcomings in data of this kind, no decision could be made as to whether the familial tendency demonstrated is genetic, and, if so, its mode of transmission. The earlier age of onset of the disease in successive generations is noteworthy.

ASSOCIATED DISEASES

Hypertension

It proved to be impossible to obtain, by specific questioning, reliable data on the presence or absence of elevated blood pressure in the families of either group.

Diabetes Mellitus

Again, the data on the prevalence of diabetes in the family were not very reliable. However, most subjects did know about relatives requiring insulin injections. The incidence of such a history tended to be higher in the coronary than in the non-coronary group (14 relatives of 99 patients as compared with 6 relatives of 99 controls, $\chi^2=2.725$, $0.05 < p < 0.1$). This tendency is in keeping with the known association of atherosclerosis and diabetes,[23] and also with the fact that coronary patients without overt diabetes often exhibit some carbohydrate intolerance.[24]

Marital Status

The marital status of the two groups was compared and the results are presented in Table VII.

TABLE VII.—MARITAL STATUS

Group	*No.*	*Single*	*Married*	*Widower*	*Separated*
Control.....	100	8	83	2	7
Coronary....	102	6	84	4	8

χ^2 (last two columns combined) = 0.701, $p < 0.75$.

There was no significant variation of this pattern when analyzed by decades.

In keeping with Yater's findings,[25] the number of married men was the same in both groups. The percentage of men who were separated was similar. There were no divorced men. Pomeroy and White[26] had previously suggested that there may be more divorces in a coronary group and that this "may or may not represent a factor of stress".

The marital status of the two groups, then, is quite similar and appears in this study to be of no significance in C.H.D.

Number of Children

The number of children of each married subject was tabulated and analyzed.

TABLE VIII.—NUMBER OF CHILDREN

Group	*n*	*None*	*1 or 2*	*3 or 4*	*Over 4*
Control.....	83	12	48	16	7
Coronary.....	84	17	42	17	8

$\chi^2 = 1.353$, $p < 0.75$.

The results (Table VIII) show that, as in a previous study,[26] there were no real differences between the two groups.

Occupation

For many years, clinicians have entertained the impression that there is an apparently higher incidence of C.H.D. among professional and managerial personnel. Although there have been some reports to the contrary,[27, 28] the bulk of epidemiological evidence both in the United States[11, 29] and in Britain[30, 31] seems to confirm this impression. The association of C.H.D. with such occupations had been ascribed to the "high-pressure intellectual activity of the occupation".[32] More recently, it has been attributed to the limited physical demands of

the occupation, the incidence being highest in men with sedentary occupations.[33]

The habitual occupations of the subjects in this study were ascertained and arbitrarily classified (Table IX). All occupational groups are satisfactorily represented. It is seen that there is no real occupational difference between the two groups. It may be added that the incidence of myocardial infarction in the Canadian armed forces is not related to rank.[34]

As in most previous studies, the subjects were drawn from a large urban centre. It is believed, however, that no bias between the two groups was thereby introduced in the selection of participants.

TABLE IX.—OCCUPATION

Group	n	Professional	Managerial	Clerical	Skilled labour	Unskilled labour	Habitually unemployed
Control	100	7	10	31	22	30	0
Coronary	102	8	10	21	26	35	2

χ^2 (excluding last column) = 2.708. p <0.75

The similarity of the composition of the two groups, then, is taken as evidence that an occupational factor (psychic or physical) is not important in the etiology of C.H.D.

Physical Activity

The traditional view, based on little scientific evidence, has been that physical activity, by increasing "wear and tear", was at least an aggravating factor in the genesis of coronary atherosclerosis. On the other hand, recent studies[35, 36] have revealed that C.H.D. is more prevalent among the sedentary than among those engaged in more active occupations.

TABLE X.—PHYSICAL ACTIVITY: PRESENT

Group	n	Minimal	Moderate	Most
Control	100	8	65	27
Coronary	102	29	51	22

χ^2 = 14.100, p <0.001.

Table X summarizes in a simple arbitrary manner the physical activity of the subjects at the time of investigation, as assessed by a consideration of recreational as well as occupational activity. A larger proportion of the coronary population is in the "minimum activity" group and this is statistically highly significant ($p < 0.001$). As emphasized in one editorial comment,[37] the usual practice of noting the last occupation of the subject, rather than the occupation in which he has spent most of his working life, may lead to fallacious conclusions. This is especially true in a study such as this, since the management of patients who have myocardial infarctions includes restriction of their physical activity. Accordingly, the "life-long activity" of the subject was assessed by inquiring into his physical activity in his childhood, youth and adult life. It is recognized, however, that not all subjects doing the same job are equally active.

TABLE XI.—PHYSICAL ACTIVITY: LIFELONG

Group	n	Minimal	Moderate	Most
Control	100	0	55	45
Coronary	102	0	39	63

χ^2 = 5.050, p <0.05* (last two columns only).

Table XI demonstrates that a significantly larger proportion of the coronary group was classified as being physically more active ($p < 0.05$). The results by decade were in keeping with this general pattern.

In this study, then, C.H.D. was associated with habitually greater physical activity. This cannot be attributed to the nature of the subjects' occupations, which have been shown to be similar in the two groups. This finding is in accord with reports of some others,[35] but is at variance with the lower death rate from coronary disease reported among manual workers[33] and among those athletes who continue to be physically active.[26] In such studies, differences in physical activity were considered to be an important factor in the pathogenesis of atherosclerosis, with little regard to other possibly important differences. The suggestion that physical exercise may be a powerful prophylactic against coronary disease[37] remains to be proved.

Athletic Activity

Earlier investigations have shown that histories of previous athletic activity were very frequent among coronary victims.[11, 39] In this study, athletic activity in school and college and throughout adult life was ascertained by direct questioning. About one-fifth of the subjects in each group had to be excluded from this analysis because they did not have the opportunity to participate in formal athletic activity.

TABLE XII.—ATHLETIC ACTIVITY: LIFELONG

Group	n	Slight	Moderate	Much
Control	83	27	33	23
Coronary	87	18	27	42

χ^2 = 7.8609, d. of f. = 2, p <0.025.*

The results are arbitrarily classified and tabulated in Table XII. It is seen that a significantly larger proportion of the coronary subjects were athletically more active than the non-coronary controls ($p < 0.025$). The same pattern as presented by the group as a whole was found to obtain when the data were analyzed by decades.

These results confirm the previously recognized association between C.H.D. and athletic activity. In this regard, however, it must be emphasized that such statistical associations do not constitute proof that physical and athletic activity *cause* C.H.D.

Past Health

For many years clinicians have had the impression that the individual particularly susceptible to C.H.D. is one who has been "especially healthy all of his life".[40] However, Jones[41] has accumulated data which led him to believe that "episodes of disease during childhood underline the tendency to succumb to internal disease (including cardiovascular disease) in later life".

To evaluate this factor, a detailed history of all previous disease was obtained by a review of the files and by direct interrogation of all the subjects. It is evident that while the coronary subjects were admitted to the study because of C.H.D., the control subjects were made available because of some other disease. This creates a bias which would make the history of non-coronary disease appear higher in the control group. To correct this bias, the illness that prompted the initial hospitalization of the control subjects was excluded. After tabulating the number and nature of all the diseases, the results were arbitrarily graded from "none" (common cold and the like) to "much", the latter denoting a history of much severe disease.

TABLE XIII.—NON-CORONARY DISEASE EXPERIENCED

Group	*n*	*None*	*Slight*	*Moderate*	*Much*
Control.....	100	20	44	30	6
Coronary.....	102	33	35	27	7

$\chi^2 = 4.429$, $p < 0.25$.

Table XIII shows the results of such grading for the two total groups. The difference between the two groups is not significant ($p < 0.25$). The results are similiar within the various decades.

It is concluded that there is no significant difference in the frequency of non-coronary disease experienced by the control and coronary groups. It may well be that the clinician, like the layman, is unduly impressed by the dramatic appearance of unheralded fatal disease in subjects who, in the recent past, have been healthy.

Tobacco

A quarter of a century ago, White,[42] after reviewing the literature and analyzing his own statistics, concluded that the use of tobacco played no important role in the genesis of C.H.D. (angina pectoris). In more recent large-scale statistical studies on American men, a positive relationship between cigarette smoking habits and the death rate from C.H.D. was found.[43] In a smaller but more homogeneous population (British physicians) a similar association was claimed;[44] however, this association was later shown to be applicable only to those under 55 and over 74 years of age.[45] In the Framingham study,[46] there was no regular progression of the coronary attack rate among men with increasing consumption of cigarettes, although very heavy smokers did show the highest incidence. In India, there is no decrease in susceptibility to C.H.D. among the Sikhs, who are forbidden by their religion to smoke.[47]

The smoking habits of the subjects in this study were ascertained by direct questioning. A few who smoked only cigars or pipes were included among the non-smokers. The smokers were divided into three categories: light (less than 10 cigarettes daily), moderate (10 to 20) and heavy (more than 20 cigarettes a day).

TABLE XIV.—NON-SMOKERS

					Total	
Decade	*4th*	*5th*	*6th*	*7th*	*No.*	*%*
Control.....	2/25	0/25	4/27	0/23	6/100	6.0
Coronary.....	1/25	1/26	2/28	1/23	5/102	4.9

Table XIV shows that the number of non-smokers constituted a very small percentage (about 5%) of each group. This low incidence of non-smokers may perhaps be due to the fact that this is a selected male veteran population who have acquired the smoking habit in the armed forces and maintained it in civilian life. Certainly, there is no demonstrable difference between these two groups.

TABLE XV.—HEAVY SMOKERS

					Total	
Decade	*4th*	*5th*	*6th*	*7th*	*No.*	*%*
Control.....	5/25	7/25	6/27	3/23	21/100	21.0
Coronary.....	12/25	4/26	5/28	2/23	23/102	22.5

Table XV concerns the heavy smokers in each group. The total numbers in the two groups are very similar. It is only in the fourth decade that there is a large proportion of heavy smokers in the coronary group (not statistically significant). This latter finding is in accord with the experience of others.[11, 25]

Of the 100 controls, 32 were "light" and 41 "moderate" smokers; of the 102 patients, 31 were classed as "light" and 43 as "moderate". The composition of the two groups is obviously similar.

It is concluded that there is no difference in cigarette consumption between the coronary and non-coronary groups, except possibly in the fourth decade where a larger number in the coronary group were heavy smokers.

Alcohol

In the past, perhaps because of moral beliefs rather than scientific evidence, alcohol was charged with being responsible for atherosclerosis.[48] It was soon found that people who never drank were not immune from atherosclerosis, and that the use of, or abstinence from alcohol played no important role in the genesis of angina pectoris.[42] Indeed, it was claimed that alcoholics suffered less atherosclerosis,[49, 50] and some came to regard alcohol almost

as an antidote to atherosclerosis.[51] Most clinical studies[11, 25, 42] have revealed no differences in the consumption of alcohol by coronary and non-coronary groups.

In this study, the amount of alcohol consumed by each subject was determined by interrogation. The usual consumption was arbitrarily graded as "heavy" if it exceeded the equivalent of three ounces of alcohol every day, "moderate" if less than this amount was taken daily, and "light" if alcohol was taken only occasionally.

TABLE XVI.—NON-DRINKERS OF ALCOHOL

					Total	
Decade	*4th*	*5th*	*6th*	*7th*	*No.*	*%*
Control	2/25	3/25	9/27	2/23	16/100	16.0
Coronary	1/25	2/26	7/28	5/23	15/102	14.7

Table XVI shows that the proportion of non-drinkers was the same in both groups in all decades. The proportions of heavy (Table XVII), moderate and light drinkers were also similar.

TABLE XVII.—HEAVY DRINKERS OF ALCOHOL

					Total	
Decade	*4th*	*5th*	*6th*	*7th*	*No.*	*%*
Control	1/25	2/25	5/27	3/23	11/100	11.0
Coronary	4/25	1/26	0/28	0/23	5/102	4.9

χ^2 (for total) = 1.806, p < 0.25.

No significant difference in alcohol consumption between the coronary and control groups exists. It is concluded that alcohol plays no real part in coronary atherogenesis.

Body Build and Weight

Some 30 years ago, Levine and Brown[39] noted that young coronary patients were often of a "robust, athenic" body build. More recently, Gertler and White,[11] rating physique by the Sheldon method of somatotyping,[12] concluded that the mesomorph (the muscular type with greater depth and breadth dimensions) was most prone to C.H.D. The necropsy studies of Spain, Bradess and Huss[53] confirmed the greater amount of coronary atherosclerosis in the mesomorphic male.

In this study, an attempt was made to determine which of the body measurements taken in "routine" clinical practice was most closely associated with C.H.D. The following measurements were recorded on all subjects: (1) height (without shoes, to the nearest half inch); (2) chest circumference (mid-sternal level, midway between inspiration and expiration, to the nearest half inch); and (3) weight (in underclothes, to the nearest half pound).

Height

It has previously been found that in middle age the death rate for C.H.D. is greater among shorter men,[54] and that young coronary patients are shorter than their non-coronary controls.[11]

Table XVIII shows that in this study the coronary subjects, as a group were significantly shorter than the non-coronary controls. The difference is present in all decades and is most impressive in the fourth decade.

The clinician, of course, is much more concerned about the individual patient than about mean values for groups of subjects. It is therefore of interest to see how well the two groups can be separated by the height measurement. It was found that 48 of the control group were below the mean height for the combined group of patients, and that 34 of the coronary group were above this mean. In short, 40.6% of the patients were misclassified by the criterion of height. Even in the fourth decade, the misclassification was 28.0%. Obviously, the criterion of height alone is of no diagnostic value.

Chest Circumference

It has been reported that the depth of the chest of young[11] and of middle-aged[55] coronary patients is greater than that of non-coronary controls.

Table XIX demonstrates that the mean chest circumference of patients in this study is significantly larger in the coronary group. The differences are greatest in the fourth and seventh decades.

Again, the attempt to discriminate between the control and coronary groups, by consideration of the chest circumference alone, involved a large misclassification (44.1%) and was obviously of no distinguishing value.

Weight

A succession of medico-actuarial studies by insurance organizations have shown an increased mortality from coronary disease in overweight people as compared to those who are underweight.[56]

TABLE XVIII.—HEIGHT (Inches)

	Control			*Coronary*				
Decade	*n*	*Mean*	*S.E.*	*n*	*Mean*	*S.E.*	*Difference Cor.-Con.*	*p*
4th	25	70.4	± .50	25	67.6	± .48	2.8	<0.001**
5th	25	68.1	± .47	26	67.4	± .57	0.7	<0.4
6th	27	68.9	± .44	28	67.0	± .64	1.9	<0.025*
7th	23	67.7	± .56	23	67.4	± .60	0.3	>0.5
Total	100	68.8	± .26	102	67.3	± .29	1.5	<0.001**

S.E. = Standard error. *Significant. **Highly significant.

TABLE XIX.—CHEST CIRCUMFERENCE (Inches)

Decade	Control n	Control Mean S.E.	Coronary n	Coronary Mean S.E.	Difference Cor.-Con.	p
4th	25	37.1 ± .56	25	38.5 ± .37	+1.4	<0.05*
5th	25	37.0 ± .48	26	38.1 ± .42	+1.1	<0.1
6th	27	37.8 ± .43	28	37.4 ± .40	−0.4	<0.5
7th	23	36.4 ± .48	23	38.0 ± .52	+1.6	<0.025*
Total	100	37.1 ± .24	102	38.0 ± .21	+0.9	<0.01**

S.E. = Standard error. *Significant. **Highly significant.

Analyses of autopsy material have both supported[57, 58] and controverted[25, 53, 58] the association of overweight and atherosclerosis. A study from the Mayo Clinic[60] showed significantly fewer atherosclerotic lesions in underweight individuals but no more atherosclerotic disease in those who were overweight than in the group with average weight.

Garn *et al.*[61] pointed out that the conclusions of earlier authors that overweight was common in younger coronary victims, were drawn from studies in which the weights of the patients were compared to insurance or army standards. Employing a control group, they themselves found that both their coronary and non-coronary subjects were "overweight" in comparison with army standards, but to the same degree.

TABLE XX.—WEIGHT (Pounds)

Decade	Control n	Control Mean S.E.	Coronary n	Coronary Mean S.E.	Difference Cor.-Con.	p
4th	25	167.9 ± 5.5	25	167.0 ± 3.9	−0.9	<1.0
5th	25	158.0 ± 4.8	26	160.2 ± 4.0	+2.2	<1.0
6th	27	165.2 ± 4.1	28	156.2 ± 3.3	−9.0	<0.1
7th	23	150.5 ± 4.5	23	155.7 ± 5.0	+5.2	<0.5

Table XX shows no significant difference or consistent trend in the mean weight between the coronary and non-coronary groups in this study. As might be expected, body weight had no discriminating value. It should be pointed out that in this study, body weight alone and not body fatness (obesity) was measured, and that weight need not necessarily be an accurate index of obesity.

The conclusion that body weight (in the absence of hypertension) is not a significant factor in C.H.D. is in keeping with the latest reports of the Framingham study[46] and of Gertler *et al.*[62]

Relationship of Chest Circumference, Height and Weight

An attempt was made to derive, as a simple measure of body type, a series of indices compounded from height, weight and chest circumference. Some indices, for example the chest circumference/height ratio of Robinson and Brucer,[63] or the height/$\sqrt{\text{weight}^3}$ of Gertler and White,[11] have been employed with the implicit assumption in each instance that the two variables are proportional and therefore that the regression line passes through the origin. In the present study, height, chest circumference and weight were all found to be normally distributed* in both the control and coronary groups and when the two groups were combined. However, none of the six possible regression lines passed through the origin or included it within its 1 in 1000 confidence limit.

An analysis of covariance of chest circumference on height was set up for the four decades of the coronary patients. No differences were detectable between the decades with respect to variances, the regression slopes or the intercepts. Since age could be ignored, the data could be legitimately pooled. A similar examination of the control data gave a like result.

A further analysis of covariance was then set up to compare the coronary and the control groups. The variances for both height and chest circumference were similar in the two groups ($F = 1.210$, $p < 0.2$, and $F = 1.295$, $p < 0.2$, respectively). The regression coefficients were similar ($F = 0.056$). Finally, a test of difference in the intercepts was found to be highly significant ($F = 14.445$, $p < 0.00015$). It thus appears that the significance of the difference between the two groups is very little enhanced by the compounding of the two measurements (height, $p = < 0.0003$, chest circumference $p = < 0.01$).

Similar analyses of covariance were set up on the other five possible regression lines, with similar results. Attempts to discriminate between coronary patients and non-coronary patients by any of the six regression lines showed a percentage of misclassification so high as to be diagnostically meaningless.

Discriminant analysis is the most efficient method of using the data on all three body measurements

*It can be shown by theoretical proofs that so long as the coefficient of variation (standard deviation ÷ mean) of a symmetrically distributed variable is small, any simple transformation of the values—such as cubing or extracting the cube root—will give a distribution that is very nearly symmetrical. In these data, the coefficients of variation are small and the distribution of the height, height^3, the weight and $\sqrt[3]{\text{weight}}$, all give excellent straight probit lines. There is nothing to be gained, therefore, by such time-consuming transformations of either of these measurements.

to distinguish the coronary patients. The discriminant function (Z) was found to be:

$$Z = 12.903C - 2.788H - W$$

where C is the chest circumference in inches, H the height in inches, and W the weight in pounds for any patient.

The mean value for Z of the coronary patients was 142.841, of the controls 126.287, and the overall mean 134.646. The percentage misclassification even by this most efficient method was 35.15%—once more, unfortunately, of no clinical value.

two methods. First, the differences were classified as zero (when the estimation was correct), positive, and negative. The results of this assessment are summarized in Table XXI, which shows no consistent trend in the different age groups and no significant differences in the totals. The second evaluation was a comparison of mean values. Table XXII shows no consistent trend or significant differences. It may be added that the age was consistently underestimated in both the coronary and control subjects and this reached statistical significance ($p < 0.05$ and $p < 0.01$, respectively).

TABLE XXI.—ESTIMATION OF AGE

Decade	*4th*			*5th*			*6th*			*7th*			*Total*		
Subjects	+	0	−	+	0	−	+	0	−	+	0	−	+	0	−
Control	5	6	8	6	7	7	4	4	14	7	6	8	22	23	37
Coronary	6	14	4	5	8	9	8	6	11	4	9	12	23	37	36

Figures refer to number of subjects: + is overestimated, 0 is correctly estimated and − is underestimated.
χ^2 (total) = 2.215, $p < 0.5$.

It is concluded that, within the range of these data, the coronary patients are, on the average, shorter and broader than the non-coronary subjects, but of similar weight. The measurement of height and of chest circumference, but not of weight, are perhaps of some significance in the study of the etiology of coronary atherosclerosis but are not sufficiently discriminating to be of diagnostic importance clinically.

Age and Apparent Age

Gertler and White,[11] as did Levine[40] before them, found it "striking to observe [in their group of young coronary patients] that the features of almost every individual appeared to be at least a decade older than the chronological age". Unfortunately, they gave no more detailed data in explanation of this observation, nor did they mention any similar study of their controls. Plotz[9] has formed the impression that young coronary patients have grey hair or are bald more often than he expected.

An estimate of the apparent age of each subject in this study was made from a simple consideration of the physical appearance and features. The chronological age was then subtracted from the apparent age and these values were assessed by

It may be concluded that there was no apparent undue physical ageing in the coronary group as compared to the control.

Psychological Factors

The part played by psychological factors (stress, strain and psychic tension) in the development or progression of atherosclerotic heart disease has long been debated. For example, Sprague[64] considered the evidence for the importance of such factors quite unconvincing, whereas Russek and Zohman,[65] in their analysis of possible atherogenic factors in young survivors of myocardial infarction, concluded that the "emotional strain of occupational origin" was the single most significant factor.

TABLE XXII.—MEAN UNDERESTIMATES OF AGE (Years)

Decade	*4th*		*5th*		*6th*		*7th*		*Total*	
	n	*Mean*	*n*	*Mean*	*n*	*Mean*	*n*	*Mean*	*n*	*Mean*
Control	19	0.37	20	0.60	22	2.27	21	0.10	82	0.87
Coronary	24	−0.08	22	0.91	25	1.00	25	2.24	96	1.03
Mean difference		−0.45		0.31		−1.27		2.14		0.16
t										0.292
p										>0.5

Negative values in the second line denote an overestimate.

Although external stresses and strains can readily be identified, the more important reaction of the individual to them is difficult to assess and impossible to quantitate. Moreover, a retrospective study cannot employ the double-blind technique to exclude bias, nor can it clearly distinguish the anxiety which is secondary to coronary disease from that which may be important in its genesis.

In this study, an attempt by the authors at qualitative description of the temperament of the subjects led to doubt about the classification of so many

individuals that it had to be abandoned. Habits such as the use of alcohol and of cigarettes, said to be indirect clues of emotional tension, did not differ (*s.v.*) in the two groups.

Again, the role of psychological factors in the genesis of atherosclerosis must remain in dispute. Perhaps only an anterograde study can resolve this dispute with confidence.

Relationship Between Family History and Body Build

In this project, as well as in previous studies,[11] family history and body build have both been demonstrated to have a relation to C.H.D. It is possible that the family tendency is mediated through body build, which has itself been shown to be familial.[66]

To explore this possibility, each decade of the coronary subjects was divided into body type according to their discriminant indices (*q.v.*). No difference was found in the incidence of coronary disease in the fathers or mothers between the higher and lower groups. It seems, therefore, that the family history of coronary disease in the patients studied operates independently of body build.

Relationship Between Athletic Activity and Body Build

In this project, as well as in previous studies,[11] athletic activity and body build have both been demonstrated to be related to C.H.D. It is possible, as suggested by Gertler and White,[11] that "C.H.D. and athletic participation may well be related only through a common factor of mesomorphy (muscular body build)".

Each decade of the coronary patients in this study has been divided into three groups according to athletic activity. The mean discriminant index of the body build of the "very" athletic group was not significantly different from the group whose athletic activity was estimated as "slight". Indeed, the trend was in the direction opposite to that expected.

It seems then that athletic activity operates independently of body build in its association with C.H.D.

SUMMARY AND CONCLUSIONS

A group of 102 male survivors of myocardial infarction, evenly distributed from the fourth to the seventh decades, was studied together with a control group of 100 healthy men selected from the same general population and matched by age. The coronary patients all had atherosclerosis of the "essential" type, that is, not accompanied by any disease associated with high blood pressure or secondary hypercholesterolemia. Both groups were also free of any major additional disease and were not receiving any dietary, hormonal or anticoagulant treatment.

Analysis of the objective observations made in these two groups, differing in the presence or absence of clinical coronary atherosclerosis, revealed that:

Their racial distribution was similar.

Coronary heart disease was more prevalent in the parents and in the siblings, especially the brothers, of the coronary patients. This was impressive in the fourth and fifth decades only. Clinical coronary disease occurred at progressively earlier ages in succeeding generations. A family history of diabetes was also more common in the coronary group.

Marital status and the number of children were similar in the two groups.

The occupations of the two groups were similar.

Physical activity of the two groups was similar, but the coronary group had participated to a greater degree in organized athletics.

Past health of the coronary group was no better (or worse) than that of the non-coronary group.

Alcohol and tobacco consumption was similar in the two groups.

With regard to body measurements, the coronary group were, on the average, significantly shorter in all decades, especially in the fourth decade. The average chest circumference was larger in the coronary patients, again especially in the fourth decade. There were no significant differences or trends in body weight between the two groups. For the three measurements (height, chest circumference and weight) taken separately, the overlap of the distributions was too large for these to be of diagnostic value in the individual subject. The discriminant function, compounding these measurements for maximal efficiency, also gave an excessive misclassification (35%).

Employing the simple criterion of apparent age, there was not the slightest evidence of premature ageing in the coronary patient.

It proved impossible, by simple interview, to assess with any precision the psychological characteristics of these subjects.

The significant differences, then, were in: family history, athletic activity, and body height and chest circumference. Statistical analyses suggested that these three factors operate independently.

It should be emphasized that the differences that existed were between the means of groups and that no clear characterization of the individual could be made.

The project was initiated by the late Dr. Harold E. Rykert, whose kind and able direction was greatly appreciated. The continued support of Professor Ian Macdonald is gratefully acknowledged. The secretarial assistance of Miss Ruth Yano has been invaluable.

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ADULT SURGICAL DISORDERS ENCOUNTERED IN CHILDREN

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THE PURPOSE of this paper is to point out the occurrence, though admittedly uncommon, of lesions occurring in children that are usually encountered only in abdominal surgery of adult patients. This will be demonstrated by the case reports of three patients seen in the author's practice in a one-year period.

CASE 1.—W.S., a 16-year-old girl, was admitted to hospital on January 13, 1960, complaining of abdominal pain of three days' duration.The pain was colicky in nature and gradually increased in severity. It was located mainly in the hypogastrium. She had no nausea or vomiting and her appetite remained good. Her bowels moved normally up to the day of admission and there was no history of bleeding per rectum.

On admission the girl was moderately ill, with a temperature of 100° F. and a pulse rate of 100 per minute. The abdomen was not distended. There was acute tenderness in the lower abdomen, greatest in the suprapubic area. The lower abdomen was quite rigid and rebound tenderness was present. No masses could be palpated and no bowel sounds could be heard. There were no hernias.

Rectal examination revealed a firm tender mass anteriorly in the pelvis, above the uterus.

An admission diagnosis of pelvic peritonitis secondary to acute appendicitis or a twisted ovarian cyst was made, and a laparotomy performed shortly after admission.

At operation a firm mass was found occupying the pouch of Douglas, and lightly adherent to the back of the uterus. This mass was about the size of a golf ball or a little larger and was located in the sigmoid colon. The mass was firm in consistence and appeared to be of an inflammatory nature with an area of necrosis on the serosal surface measuring 2 cm. in diameter.

On the assumption that this was an inflammatory mass, possibly secondary to foreign body perforation, the sigmoid was mobilized and the involved segment exteriorized. The lesion was excised, leaving a double-barrelled colostomy. Much to our surprise the pathologist reported this lesion to be a moderately well differentiated adenocarcinoma of the colon.

Because this was not considered to be an adequate cancer operation, the patient was returned to the operating room on February 5, 1960, and the colostomy, along with the remaining sigmoid and descending colon and their mesentery, was resected, dividing the inferior mesenteric artery close to the aorta. An end-to-end anastomosis was then made between the splenic flexure and the upper rectum. The liver was found to be free of metastases at this operation.

The patient made an uneventful recovery and was discharged from hospital on February 17, 1960. The pathologist could find no evidence of residual tumour in the colon or its mesentery. Subsequent sigmoidoscopic examination and barium enema revealed no evidence of polyps or other lesions in the large bowel.

The patient remained well eight months later.

DISCUSSION

Although benign adenomas and polyps of the colon and rectum are common in children, carcinoma is most uncommon under the age of 20. A recent review of the literature reveals 189 cases of carcinoma of the rectum and over 80 cases of carcinoma of the colon reported in patients under the age of 20 years.[1] It is said that the prognosis in these patients is extremely poor because these tumours are of a high grade of malignancy, and local extension, lymph node involvement, or distant metastases are common findings at operation. To date no five-year survivals have been reported under the age of 16 and only two cases have been reported between the ages of 16 and 20. The longest survival on record is of an 18-year-old boy who survived eight years and in whom one mesenteric lymph gland contained metastatic disease. The youngest patient in whom carcinoma of the colon has been reported is a 9-month-old female infant with carcinoma of the descending colon.

As in adults, the commonest site for the lesion is in the rectum, the sigmoid being the next commonest. The pathology is similar to that of the adult lesion, with the one exception that mucoid carcinoma accounts for 50% in the younger group and only 5% in the adult.

The clinical picture in the young patient, however, is somewhat different from that in the adult. The commonest symptom is abdominal pain, which is frequently vague and generalized; and rectal bleeding is considered to be uncommon. Many of these young patients are operated upon for appendicitis, either acute or chronic, and frequently the tumour is missed and a normal appendix is removed. It is only after continued trouble that the diagnosis is finally made, usually at a stage when the disease is incurable. It has been emphasized that when the appendix is normal the bowel should be carefully examined for these uncommon tumours. Unfortunately this is usually impossible through a McBurney's incision.

One might expect that a large number of these patients with carcinoma of the colon under the age of 20 would be persons with familial multiple polyposis or ulcerative colitis, as these diseases are associated with malignant complications at an early age. However, Chappell,[2] in a review of 88 cases of carcinoma of the colon in patients under the age of 20, found only seven in patients with ulcerative colitis and none in patients with polyposis. It is also pointed out that malignant degeneration of a solitary polyp is extremely rare.

The treatment of carcinoma of the colon in young patients differs in no way from the treatment in the adult cases.

CASE 2.—B.G., a 15-year-old boy, was admitted to hospital on January 6, 1960, with severe epigastric pain of three or four hours' duration. This pain was steady in nature, did not radiate, and was not relieved by meperidine (Demerol), 50 mg. It was partially relieved when the patient sat up and leaned forward. He had vomited two or three times since the onset of pain. Bowel movements had been quite regular and there was no history of jaundice.

Over the previous two years he had experienced several milder attacks of upper abdominal pain and vomiting, not particularly related to meals or any specific food.

On admission the patient was an acutely ill, extremely obese boy weighing about 212 lb. His skin was pale but there was no evidence of jaundice. Pulse rate was 70 per minute and blood pressure 150/90 mm. Hg. The heart and chest were normal. His abdomen was quite obese but not distended. Acute tenderness was noted in the epigastrium, with rebound tenderness across the upper abdomen. There was no rigidity of the abdominal wall and no masses could be palpated. Bowel sounds were absent. Rectal examination was normal.

White blood cell count was 22,300 per c.mm. and serum amylase value was 755 units. A plain radiograph of the abdomen revealed no free air under the diaphragm, and no other abnormalities were noted.

A provisional diagnosis of acute pancreatitis was made and conservative therapy, including gastric suction and administration of intravenous fluids, sedation and methantheline bromide (Banthine) 50 mg. every six hours, was started. After two or three days of this therapy the signs and symptoms subsided and the amylase value returned to normal.

Oral cholecystography, on January 20, failed to demonstrate a gallbladder shadow. The procedure was repeated the next day with the same results. On January 22, intravenous cholangiography was performed. The common duct was visualized and appeared normal in calibre, and no stones were demonstrated in the duct. Several small calculi were demonstrated in the fundus of the gallbladder. Blood studies to detect the presence of congenital hemolytic anemia were negative.

On February 2, 1960, an operation was performed through a right upper paramedian incision. There was moderately extensive fat necrosis scattered over the omentum, parietal and visceral peritoneum. The pancreas was enlarged two or three times its normal size. The gallbladder was subacutely inflamed and contained about 30 small cholesterol stones. Cholecystectomy was performed and the common duct explored. No stones were found in the duct and a No. 5 dilator passed readily through the ampulla. A T-tube was left in the duct.

This patient made an uneventful postoperative recovery and his T-tube was removed on the 8th postoperative day. He has had no further attacks eight months after operation.

DISCUSSION

Acute pancreatitis is usually considered to be a disease of middle age and to be frequently associated with obesity, cholelithiasis and alcoholism. It is rarely encountered in children.[3, 6] On reviewing the medical literature, Blumenstock, Mithoefer and Santulli[5] report only 35 cases of acute pancreatitis in children. The youngest patient they found was an 8-month-old infant, who incidentally recovered after operation.

In the majority of cases the etiology is unknown. In children, unlike adults, associated biliary tract

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disease is extremely rare. A small number of cases followed trauma to the abdomen and in three or four cases roundworms were found obstructing the bile or pancreatic ducts. Gibson and Haller[4] report a case of acute pancreatitis associated with congenital bile duct cyst.

The clinical picture is similar to that in adults, and the treatment is conservative initially, when a correct clinical diagnosis is made. In the case reported, subsequent biliary tract surgery resulted in the relief of further attacks.

CASE 3.—S.B., a 13-year-old girl, was admitted to hospital on September 26, 1960, the chief complaint being upper abdominal pain and vomiting. For the previous eight months she had experienced recurring bouts of rather colicky upper abdominal pain of several hours' duration. These occurred as often as two or three times a week. The attacks were frequently in the evening and on occasion had even awakened her from sleep. There was no history of specific food intolerance, jaundice or clay-coloured stools. She had no urinary symptoms, and her menses had not yet begun.

On admission the patient was an obese, healthy appearing young girl with normal pulse and temperature. Her skin and sclerae were clear, with no evidence of jaundice. Heart and chest findings were normal.

Her abdomen was obese but not distended. There was marked tenderness and some guarding in the right upper quadrant. No masses could be felt and there was no rebound tenderness. Rectal examination was normal. Urine was normal. A white blood cell count was 11,250 per c.mm.

The next day intravenous pyelography was performed. Both kidneys functioned normally but there was gross blunting and dilatation of the middle calyces of the right kidney. Because of these findings, cystoscopy and retrograde pyelography were performed on September 30. The bladder was found to be normal, and again the dilatation of the middle calyces of the right kidney was noted. However, the consultant urologist did not feel that there was significant ureteropelvic obstruction or that her symptoms were of renal origin.

Oral cholecystograms were taken on October 3 and again on October 4. Both examinations failed to demonstrate a gallbladder shadow.

A provisional diagnosis of cholelithiasis was made, and on October 5 an operation was performed through a right upper paramedian incision. The gallbladder was found to be small but quite thick-walled, and a small stone 0.7 cm. in diameter was palpable in its neck. The common duct and pancreas were normal. A cholecystectomy and appendectomy were performed. The patient made an uneventful recovery.

DISCUSSION

Although gallbladder disease is found most commonly in older patients, it is not uncommon to find cholecystitis and cholelithiasis in younger patients, particularly young women in the postpartum period.

Approximately 500 cases of cholecystitis with or without cholelithiasis have been reported in children. Despite this, it is a diagnosis which is rarely considered when one is confronted with a child complaining of recurring upper abdominal pain. It is possible that many more cases are missed because of failure to carry out x-ray examination of the biliary tract in these young patients.

The management of gallbladder diseases in children is essentially the same as that in the adult. Cholecystectomy is the treatment of choice and cholecystostomy, previously recommended for children, has fallen into disrepute. One must also keep in mind the possibility that gallbladder stones in children may be secondary to congenital hemolytic anemia. Appropriate blood studies must always be made in these young patients. If this condition is found, splenectomy should also be carried out, preferably before any biliary tract surgery.

CONCLUSION

In the differential diagnosis of abdominal pain in children, one is accustomed to think primarily of such common lesions as acute appendicitis, mesenteric adenitis, intussusception, hydronephrosis and congenital anomalies such as Meckel's diverticulum. In these young patients one rarely considers the possibility of "adult disease". All too frequently a needless appendectomy may be performed, in which a normal appendix is removed and an uncommon but more important lesion is overlooked. Three instances of such uncommon lesions in children seen in the author's practice over a one-year period are reported. These were carcinoma of the colon, acute pancreatitis and cholelithiasis. All three patients were treated surgically with satisfactory results; the same principles were employed as in adult surgery.

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OXYTOCIC EFFECTS OF DIMENHYDRINATE* IN OBSTETRICS†

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SEVERAL INVESTIGATORS[1] have observed the sedative and anticholinergic properties of certain antihistaminic compounds and have compared their action to that of atropine, hyoscine and strophanthus. Others[2] have noted the quinidine-like effects and the analgesic effects of certain antihistaminics and have concluded that their analgesic effectiveness is between that of aspirin and pethidine. That dimenhydrinate is a valuable adjunct to anesthesia, not only in the prevention of postoperative nausea and vomiting but also in potentiating the effect of analgesic agents, has been shown by numerous workers.[3-6] These studies suggested that an antihistaminic agent such as dimenhydrinate might also be useful as a sedative and analgesic in the management of labour.

PRELIMINARY STUDIES

In our first group of 12 patients treated by dimenhydrinate (Gravol) unexpected and undesirable results were encountered. Three patients had prolonged labour for no reason that could be determined other than the antihistamine therapy. Two patients who were in satisfactory labour with dilated and effaced cervices went to sleep, and their pains gradually spaced themselves wider apart and eventually ceased completely. Labour was reinduced with an oxytocin drip and the patients then proceeded normally to full dilatation and delivery.

Since this suggested that dimenhydrinate might have an "antioxytocic" activity, it was considered that the drug would be of value in the management of threatened abortion. The study was therefore re-oriented to determine the effects of dimenhydrinate in patients with threatened abortion. It soon became evident that only in patients showing lethargy or sedation on antihistamine therapy could one expect quiescence of the uterus in those who were threatening to miscarry. In this selected group satisfactory results were obtained. Seven of 68 cases (10%) terminated in missed abortions. When the missed abortions were eventually terminated, intact ova with leathery trophoblasts were found which had been dead for some weeks. In other words, the sedated uteri had failed to expel their dead contents. In all these patients the daily oral dosages of dimenhydrinate varied between 250 and 1000 mg.

The next problem was to evaluate the efficacy of dimenhydrinate in the management of premature labour. Only three patients were included in this category, but the results were of interest. In the first case at 32 weeks and in the second at 35 weeks, both patients went to sleep after dimenhydrinate therapy, their pains spaced out and eventually ceased, and although they had effaced cervices there was no cervical dilatation. These patients carried their babies for several more weeks before giving birth to viable infants. The third patient at 28 weeks went into a steady, plodding, deliberate labour, which ended in full dilatation and expulsion of a fetus too immature to live. This patient received 1000 mg. dimenhydrinate intravenously and intramuscularly without any obvious sedative effects, over a period of 12 hours.

OXYTOCIC STUDIES

The study of the effect of dimenhydrinate upon the duration of labour was carried out on 137 patients divided into three groups. One group received oxytocin alone, another received dimenhydrinate (Gravol) alone, and the third received a combination of oxytocin and dimenhydrinate. Dimenhydrinate was administered as an intravenous drip, 250 mg. in 500 c.c. of saline, while oxytocin was given by the same route at a concentration of 5 units in 500 c.c. of saline. The third group received a combination of 250 mg. dimenhydrinate and 5 units of oxytocin in 500 c.c. of saline as an intravenous drip. These intravenous drips were all started at 20 drops per minute and the rate was increased half-hourly until sustained contractions developed. Secobarbital 200 mg. with pethidine 100 mg., or half doses of each in the same proportion, were used consistently for sedation and analgesia, and were administered as often as necessary. Dosages of up to 1000 mg. dimenhydrinate were administered within eight-hour periods and on occasion at the rate of 120 drops per minute without abnormal side effects or reactions.

RESULTS

The results obtained in 137 patients are summarized graphically in Fig. 1. This graph is essentially a distribution curve of the number of patients delivering within a given time interval (class interval = 4 hours) for each of the three treatments employed. As there was no significant difference in the distribution curves for primiparas

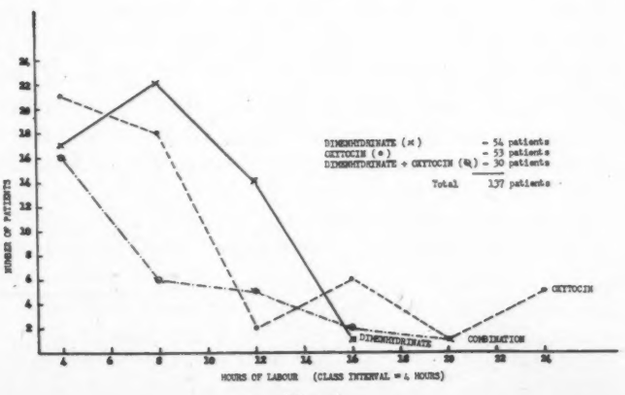

Fig. 1

*Gravol (Horner).
†Read before the Section of Obstetrics and Gynecology of the Royal College of Physicians and Surgeons of Canada, Montreal, January 1960.

as compared with multiparas, these have been grouped together in this graph.

All 54 patients who received dimenhydrinate as the induction agent delivered by the 16th hour in contrast to the 53 who received oxytocin. With this latter agent there was a group of patients who did not deliver until after 16 hours and in whom labour continued for 24 to 28 hours or more.

TABLE I.—MEAN DELIVERY TIME IN HOURS

	Dimenhydrinate (Gravol)	*Oxytocin (Pitocin)*	*Dimenhydrinate + Oxytocin*	*95% necessary difference between means*
Gravida 1.....	8.1 (27)	10.0 (22)	9.8 (14)	5.6 hrs.
Gravida 2	5.8 (15)	12.8 (23)	3.5 (6)	
Gravida 3 +	7.1 (12)	8.2 (10)	5.5 (10)	
	7.0 hrs.	10.3 hrs.	6.3 hrs.	
Delivery 1 - 10 hrs.				
Gravida 1	6.5 (18)	5.1 (12)	6.4 (9)	4.4 hrs.
Gravida 2	4.4 (12)	6.5 (20)	3.5 (6)	
Gravida 3 +	5.0 (9)	5.4 (7)	3.9 (8)	
	5.3 hrs.	5.7 hrs.	4.6 hrs.	
Delivery > 10 hrs.				
Gravida 1	11.5 (9)	21.3 (10)	14.5 (5)	10.7 hrs.
Gravida 2	11.3 (3)	20.4 (3)	———	
Gravida 3 +	13.3 (3)	26.7 (3)	12.0 (2)	
	12.0	22.8	13.3	

Table I illustrates the difference between these treatments in terms of average duration of labour. The mean delivery time for those patients receiving dimenhydrinate or dimenhydrinate plus oxytocin was three hours shorter than for those receiving oxytocin alone. While the difference was not statistically significant, it was certainly of clinical importance.

These data were further analyzed on the basis of the difference in population distribution suggested from inspection of the curve (Fig. 1) and from consideration of the physiology of uncomplicated labour. It was evident that, regardless of treatment, the majority of patients delivered within a 10-hour period, the same time interval in which a normal labour would terminate.

Table I includes, therefore, the mean duration time of labour of these patients who delivered within 10 hours, separate from those who delivered in excess of this time interval. As suggested from the distribution curve, there was no statistically significant difference between treatments during the first 10 hours of labour. Patients who delivered during this interval did so without apparent influence on their labour by the drugs employed. However, in those cases where 10 hours or more were required for delivery, dimenhydrinate as an induction agent significantly ($P = 0.05$) reduced the labour time by nearly 11 hours.

The use of oxytocin in combination with dimenhydrinate also markedly reduced the duration of labour (nine hours) but owing to the small number of patients so treated, this difference was not significant. In addition, the use of dimenhydrinate with oxytocin produced a much smoother induction, with less vicious contractions than usually encountered with oxytocin alone.

These data demonstrate that in an unselected group of 137 normal deliveries the use of dimenhydrinate as an oxytocic agent, compared with oxytocin, significantly shortened the duration of labour in those patients in whom labour continued for 10 hours or more. Essentially similar results were obtained with the use of dimenhydrinate in combination with oxytocin as were observed with dimenhydrinate alone.

It would appear from the above data that, where oxytocin alone was used as an induction agent, the sharp unrelieved pains produced resulted in distress. This in turn produced inhibition of labour by a subconscious effort to reduce pain. Prolongation of labour resulted.

CONCLUSION

Dimenhydrinate (Gravol), an antihistamine and antinauseant, has been demonstrated in this study to have an oxytocic effect on the full-term uterus. Addition of dimenhydrinate to an oxytocin drip for induction resulted in a smoother, shorter labour. The vicious contractions experienced with an oxytocin drip are seldom encountered when dimenhydrinate is added.

As seen from the preliminary studies in patients with threatened abortion and premature labour, the use of dimenhydrinate as an antiemetic produced no undesirable effects on the pregnant uterus or on the fetus. The oxytocic effect of the compound was seen only on the full-term uterus. Dimenhydrinate is a safe antinauseant and oxytocic agent in doses up to 1000 mg.

The assistance of Dr. J. D. McColl of Frank W. Horner Limited in the statistical analysis of these data was most appreciated.

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TREATMENT OF BACTERIAL ENDOCARDITIS BY ORAL PHENETHICILLIN POTASSIUM (SYNCILLIN)

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SUCCESSFUL treatment of subacute bacterial endocarditis by oral penicillin V has been previously reported.[1-5] Early reports[6-8] on the excellent absorption and antibacterial activity obtained with oral phenethicillin suggested that it should be equally useful in the treatment of bacterial endocarditis due to penicillin-sensitive organisms. The following is an account of its successful use in the treatment of three patients.

MATERIALS AND METHODS

Phenethicillin,‡ a newly discovered semisynthetic penicillin, is the potassium salt of 6-(alpha-phenoxypropionamido) penicillanic acid. It was administered as compressed tablets containing 250 mg., molecularly equivalent to 400,000 I.U. of penicillin G.

In two cases *Streptococcus viridans* was the causative organism, and in the other, *Streptococcus faecalis*. Sensitivity studies to commercially available antibiotics were determined by the agar disc technique. Minimal inhibitory concentration (M.I.C.) was obtained by the serial dilution technique. The serum levels of phenethicillin were determined in the Bristol Laboratories, Syracuse, N.Y., by the plate diffusion method, using *Sarcina lutea* as the test organism.

In order to evaluate the possible toxicity of this new drug, the following laboratory determinations were undertaken before and during therapy: complete blood count, platelet count, urinalysis, non-protein nitrogen, prothrombin time, thymol turbidity and serum transaminase.

CASE REPORTS

CASE 1.—M.T., a 27-year-old general contractor, was admitted to hospital on May 27, 1960. He was known to have a tetralogy of Fallot in mild form, and an episode of bacterial endocarditis with negative blood cultures had been successfully treated one year previously by aqueous penicillin G given over a period of three weeks. The patient resumed normal life and was relatively well until one month before this admission, when general malaise, sore throat, fatigue, anorexia and fever appeared. He had had a tooth extraction one week before the onset of this illness. His family physician prescribed oral chloramphenicol during the 10 days before referring him, but the patient's temperature continued to rise to 100-101° F. every evening. Mild hemoptysis occurred several days before admission. He lost over 10 lb. during that time.

The patient did not appear chronically ill. Several petechiae were noted on the buccal mucosa and two splinter hemorrhages were observed under the third and fifth right fingernails. The fundi, on examination, showed no petechiae. There was slight digital clubbing but no cyanosis. Blood pressure was 130/75 mm. Hg and the heart rate was regular at 120 per minute. The lungs were clear. A thrill and a loud systolic murmur were noted over the entire precordium, with maximal intensity at the third left intercostal space. The spleen extended downward over two finger-breadths and was tender. The liver was not enlarged and there was no pedal edema. The routine laboratory tests, urinalysis, non-protein nitrogen (NPN) determination, fasting blood sugar value and Kahn test were normal. The hemoglobin value was 13 g. %, the white blood cell count was 8700 per c.mm. and the corrected sedimentation rate was 29 mm. in one hour. The C-reactive protein value was 3+; antistreptolysin "O" titre was 12 units. Serum protein electrophoresis showed decreased albumin and beta globulin fractions and increased gamma globulin (34.7%). Bleeding time was seven minutes. Throat and nose cultures yielded a normal flora, and urine culture was negative. Five blood cultures of samples taken the evening of admission and the next morning grew *Streptococcus viridans* sensitive by the disc technique to penicillin, erythromycin, chloramphenicol, the tetracycline derivatives, novobiocin, oleandomycin and kanamycin. The minimal inhibitory concentration (M.I.C.) of phenethicillin was subsequently found to be 0.78 μg./ml. The electrocardiogram showed right axis deviation and right ventricular hypertrophy. The chest roentgenogram revealed normal pulmonary parenchyma, decreased pulmonary vascularity and slight cardiomegaly with a cardiothoracic ratio of 15:28.5.

The oral temperature varied between 99 and 100.4° F. until the third day, when it became normal after oral phenethicillin was begun. He was given 1 g. of phenethicillin every four hours for two days. This was reduced to 5 g. daily by omitting the 4 a.m. dose, and it was continued in this manner for the next 11 days. During the first six days of treatment, he complained of nausea, occasional emesis and mild diarrhea. These gastrointestinal disturbances were readily controlled by administration of proclorperazine and a kaolin-pectin preparation. Subjective improvement became evident by the fourth day of treatment. The petechiae disappeared, but the spleen was still palpable one finger-breadth below the costal margin when the patient was discharged after 16 days of care. At home he continued to take 5 g. of phenethicillin daily for one week and 3.75 g. during the fourth and last week of therapy. The serum concentration values of phenethicillin are shown in Fig. 1. Urine NPN value, platelet count, thymol turbidity value and serum transaminase level were within normal limits before the patient was discharged from hospital. The hemoglobin value was 13.7 g. %, the white blood cell count 5200 per c.mm., the C-reactive protein 1+, and the corrected sedimentation rate was 27 mm. in one hour. One blood culture was reported as negative.

The patient was seen at the office on June 1 and 14, July 6, August 3 and October 3, 1960. He had gained 15 lb. since the onset of treatment and had no complaints. The splinter hemorrhages had disappeared and

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‡Phenethicillin (penicillin 152 marketed as Syncillin) has been generously supplied by the Bristol Laboratories of Canada Limited.

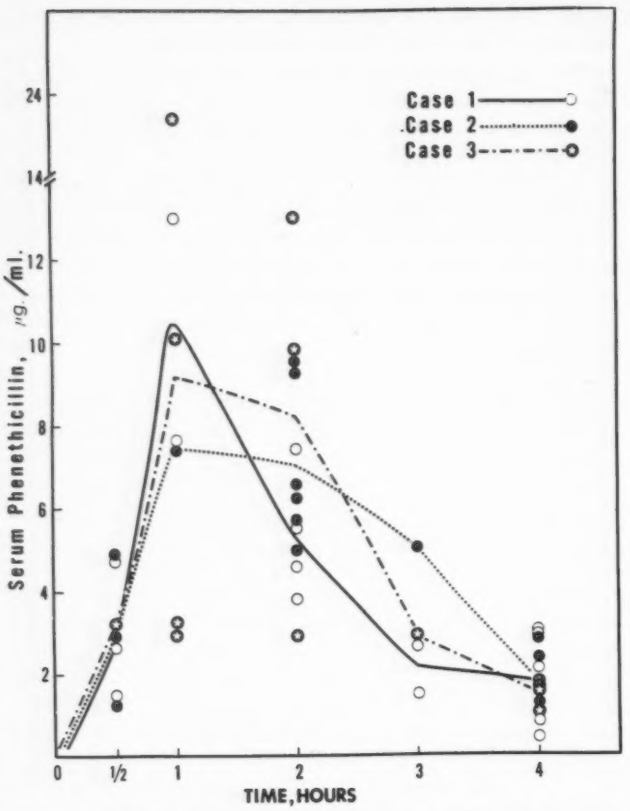

Fig. 1.—This figure illustrates the satisfactory serum levels of phenethicillin after administration of 1 g. of oral phenethicillin potassium.

the spleen showed no enlargement. The hemoglobin level subsequently rose to 14.5 and to 16.1 g. % at his last visit. Serum protein electrophoresis on June 14, two weeks after discontinuation of the drug, showed a slight elevation of the gamma globulin fraction (21.4%). The C-reactive protein value and the sedimentation rate obtained at each visit became normal on August 3, two months after cessation of treatment. The auscultatory findings, electrocardiogram and heart size had not changed.

CASE 2.—This 34-year-old male designer (C.M.) was admitted to hospital on May 6, 1960. He had been evaluated at the Institute of Cardiology in 1956 for a heart illness which had been discovered during a routine preschool examination. On physical examination, complete absence of body hair was noted. The blood pressure was 150/40 mm. Hg. A systolic thrill was present over the left sternal border at the third intercostal space. Loud systolic and diastolic murmurs were heard at the left sternal border and at the cardiac apex. The rhythm was regular. There was no sign of congestive failure. The blood Wassermann test was positive, but the spinal fluid test was normal. Right heart catheterization revealed findings compatible with ventricular septal defect. The discharge diagnoses were ventricular septal defect, associated aortic insufficiency and treated Wassermann-fast syphilis.

The patient was not seen until November 1959, when he visited the office because of frequent palpitations, fatigue, retrosternal pain and dyspnea on exertion. He was given digitalis and quinidine and improved somewhat. In March, he experienced general malaise, cough and possibly fever of several weeks' duration. Following this "grippe", he remained tired and anorexic and began losing weight. In mid-April, he experienced severe pain over the left chest and below the left costal margin. At the office two days later, a small left pleural effusion was found in addition to basal rales, hepatomegaly and pedal edema. He was advised to remain in bed and to take his temperature twice daily. When he reported a persistently elevated temperature, bacterial endocarditis was suspected and a blood culture, hemoglobin and white blood cell count were requested. It was subsequently learned that he had undergone a tooth extraction in early November 1959. He had lost 14 lb. during these prior six months.

On admission, he was pale and appeared chronically ill. The oral temperature was 102° F., blood pressure 180/30 mm. Hg and pulse 96 per minute. There were no petechiae, Osler's nodes or splinter hemorrhages. The pupils reacted normally to light and to accommodation. Funduscopic examination revealed no petechiae. The carotid arteries were markedly pulsatile. There were no palpable lymph nodes. Subcrepitant rales were present over the left lung base. The heart rhythm was regular. The murmurs previously described were unchanged. The liver was not enlarged, but the spleen extended three finger-breadths below the costal margin. He had no pedal edema. Deep tendon reflexes were normal.

The urine contained hyaline and granular casts, a few leukocytes per high-power field but no pus cells. NPN, fasting blood sugar and white blood count values were normal. The hemoglobin value was 9.5 g. % and the hematocrit 31%. A corrected sedimentation rate was 33 mm. in one hour and C-reactive protein 3+. Serum protein electrophoresis showed decreased albumin and increased gamma globulin (27.6%). The chest roentgenogram showed blunting of the left costodiaphragmatic angle, increased vascular markings and a greatly enlarged heart with a cardiothoracic ratio of 20.5:30. The electrocardiogram was unchanged except for signs of digitalis effect; it showed left ventricular hypertrophy. Three blood cultures of samples taken on separate days grew *Streptococcus viridans*. The agar disc sensitivity test was positive for penicillin, erythromycin, chloramphenicol, the tetracycline drugs, novobiocin and oleandomycin. The organism was inhibited by 0.1 µg./ml. of phenethicillin (mean M.I.C.). The minimal inhibitory concentration (M.I.C.) of penicillin V and penicillin G was 0.006 µg./ml.

Treatment with phenethicillin was begun on the second hospital day, at a dose of 6 g. daily, 1 g. every 4 hours. Definite subjective improvement followed and the oral temperature did not rise above 99.6° F. Because of the severity of the heart disease and the long duration of the infection, which appeared to have been present for six months, it was decided on the fifth hospital day to add streptomycin, 1 g. daily, to his antibiotic treatment. With this regimen, the temperature became and remained normal thereafter. At first, the patient complained of nausea while taking the tablets, but this did not occur when they were taken with ginger ale. Diarrhea was quickly controlled at the onset of therapy by kaolin-pectin. The phenethicillin was decreased to 5 g. daily on the 8th day. He was discharged on May 27, but continued taking the drug in the same amount until June 4. He received phenethicillin for a period of four weeks and streptomycin for 17 days. The serum blood levels of phenethicillin are shown in Fig. 1. The urine and NPN value were normal. Transaminase and thymol turbidity values

remained normal. A blood culture had been reported negative before discharge. The auscultatory findings, electrocardiogram and heart size had not changed.

The patient was examined at the office on June 15, 1960. He had been entirely afebrile and his appetite was excellent. He still complained of being easily fatigued and of palpitations and dyspnea with the slightest activity. On June 13, the left ankle and left hypothenar eminence became swollen and painful. He also complained of ataxia but had no other neurological symptoms. His weight had not changed. Blood pressure was still 140/40. There were no petechiae, Osler's nodes or splinter hemorrhages. The left hypothenar eminence was swollen and tender, but the left ankle appeared normal. His spleen was not palpable. There was no nystagmus, the finger-nose test was normal and there was no Rhomberg sign. The hemoglobin level was 12.3 g. %, the white blood count 8900 per c.mm., the corrected sedimentation rate 31 mm. in one hour and the C-reactive protein 3+. Serum protein electrophoresis gave normal values. Blood culture was negative.

It was felt that the swelling of the hypothenar eminence and left ankle was possibly due to aseptic emboli but that the infection was cured. The ataxia was believed to have been caused by the streptomycin, and the patient was scheduled for vestibular apparatus function studies. On June 23, 1960, he was awakened by a severe headache and neck stiffness. En route to the Institute, he became extremely dyspneic and subsequently unconscious. He was brought to the Montreal General Hospital emergency room and admitted to that hospital. On arrival, he was found in acute pulmonary edema, extremely pale, with a blood pressure of 250/0 and a pulse of 175/minute. Five hours later, he was free of pulmonary edema but there was stiffness of the neck, a left hemiparesis and an upgoing left toe. The spleen and liver were not palpable and no splinter hemorrhages were present. The lumbar puncture revealed grossly bloody fluid. On June 26, it was recorded that the patient had been oliguric since admission and this was noted to have persisted. His urine at time of admission had a specific gravity of 1.013; it contained protein, 20 to 25 red blood cells, a few white cells and granular casts per high-power field. The hemoglobin value was 9.8 g. % (phlebotomy had been performed). The BUN value was 89 mg. % on June 28 and 125 mg. % on June 30. The patient became more deeply unconscious, had localized seizures and died on July 1, 1960.

Pertinent autopsy findings.—The heart weighed 730 g. and was enlarged in all its dimensions. There was a large perforated aneurysm of the right sinus of Valsalva that presented itself in the right ventricular outflow tract which it partially obstructed. A small high interventricular septal defect was noted. The aortic valves were distorted and calcified. The right cusp was retracted, adherent to the interventricular septum and partially occluded the septal defect. In the adjacent non-coronary cusp was an oval 1.5 x 1.0 cm. perforation with slightly thickened and rounded margins, about which were irregular papillary and verrucous vegetations. They were firmly attached and fibrotic in consistency, partly pale and partly dark red in colour. The left coronary cusp showed a 4 x 2 mm. oval perforation with slightly thickened and rounded margins. The microscopic studies of the aortic valve showed no evidence of inflammatory cell infiltration, and no bacteria were found in the vegetations composed of organizing and calcific fibrinoid material. The cultures of heart blood taken at autopsy yielded micrococci (but no *Streptococcus viridans*). The spleen was of normal size, but there was a small old infarction.

A massive right temporal lobe cerebral hemorrhage was described. "The middle cerebral artery could be traced around this cavity and appeared normal, free of arteriosclerosis or of any other lesion. No mycotic aneurysm was detected in the wall of the cavity though it would be easy to miss one." The appearance of the kidneys was that of "acute nephrosis, essentially of the lower nephron or hemoglobinuric type, but with acute degenerative changes throughout the convoluted tubules as well. There was no evidence of glomerular or other focal embolization, or evidence of pre-existing renal disease."

The lungs showed passive congestion and edema, acute bronchiolitis and early pneumonia of the right lower and left upper lobes.

Comments.—It seems that the bacterial endocarditis was cured clinically and bacteriologically. Furthermore, the autopsy findings did not reveal evidence of an active infection of the aortic valve or of any other heart structure; the description was compatible with healed bacterial endocarditis. The presence, during the previous four years, of an aortic run-off due to aortic valve regurgitation, possibly with associated perforation of the aneurysm of a sinus of Valsalva, suggests that the patient may have had previous episodes of bacterial endocarditis. It is probable, however, that the aneurysm was congenital in origin; the perforation may have been spontaneous or it may have been due to the endocarditis. The cause of the cerebral hemorrhage is not known, but a ruptured mycotic aneurysm was not definitely excluded. The acute lower nephron nephrosis does not appear to have been related to the bacterial endocarditis.

CASE 3.—This 39-year-old Italian housewife (L.R.) had been operated upon four years previously for mitral stenosis. She had been greatly improved and was still doing well when last seen at a routine follow-up visit in June 1959. Her blood pressure had remained in the range of 100-200/70-80 since her operation. Atrial fibrillation was present with a ventricular rate of 90 per minute. The second pulmonic sound was loud and reduplicated. Grade I/IV systolic and grade II/IV diastolic murmurs were heard at the left side of the sternum. A diastolic rumble was noted at the apex but there was no systolic murmur. The first sound at the mitral area was slightly increased and an opening snap was still present. She was admitted to hospital on May 27, 1960, because of a recent illness of five days' duration. She complained of general malaise, vomiting and chills, and had a fever of 101 to 104° F. She experienced moderately severe pain in the left flank radiating to the left buttock and thigh. There were no gastrointestinal, respiratory or urinary symptoms, except for polyuria. She had had tooth extractions three months, and six weeks previously. A furuncle on the back had improved after one week of local therapy.

On examination, several petechiae were noted on the soft palate and buccal mucosa but there were no

splinter hemorrhages or Osler nodes. The blood pressure was 120/70 and an irregular heart rhythm at 100 per minute was noted. The auscultatory findings were unchanged. The spleen was palpable two finger-breadths below the left costal margin. There was no costovertebral tenderness. Her urine contained a few red blood cells and numerous bacteria, but no pus. The hemoglobin value was 13 g. %, the white blood cell count 7550 per c.mm. and the corrected sedimentation rate was 44 mm. in one hour. Serum protein electrophoresis showed slightly decreased albumin and beta globulin fractions and an elevated gamma globulin (25.5%). The C-reactive protein value was 1+. The antistreptolysin "O" titre was 166 units and the heterophile-antibody titre, 1:4. Culture of a throat specimen grew *Streptococcus viridans* and of a nose specimen, *Staphylococcus albus*. Three blood cultures yielded enterococcus sensitive by the plate disc technique to penicillin, erythromycin, chloramphenicol and the tetracycline drugs. The M.I.C. of phenethicillin was subsequently reported at 0.78 μg./ml. The electrocardiogram showed right axis deviation, atrial fibrillation with a controlled ventricular rate and non-specific ST-T changes. The roentgenogram of the chest revealed moderate cardiomegaly with a cardiothoracic ratio of 15.5:28, but was otherwise normal. The temperature varied from 98 to 101° F. during the first four days. Phenethicillin therapy, 1 g. every four hours, was begun on the fourth day, May 31. This amount was reduced to 5 g. daily by omitting the 4 a.m. dose on the 10th day of therapy. The patient felt better by the second day of treatment, and continued to improve subjectively. On June 6, new petechiae appeared on the palate. By June 18, she was still feeling well, two blood cultures had been reported negative, but her spleen was still palpable and the corrected sedimentation rate was elevated at 44 mm. in one hour. Because of these findings and the usual resistance of this type of organism, the drug was increased to 9 g. a day, 1 g. every two hours, except during the night. This regimen was continued for seven days. The serum phenethicillin levels are shown in Fig. 1. The average serum level one hour after intake at the time when the drug was administered every two hours was 12.4 μg./ml. Except for mild nausea on the first day of treatment, she suffered no other untoward reaction, even with the large amount taken during the last week. Urinalysis and determination of NPN, thymol turbidity and serum transaminase values and white blood cell count and platelet count were repeated on the 11th day of treatment: the results were within normal limits. The serum potassium level did not rise above 5.5 mEq./l. The patient was discharged after 25 days of treatment. The blood pressure had remained at 110-100/70-50. The auscultatory findings, the electrocardiogram and the chest roentgenogram had not changed.

This patient was seen at the office on July 5, July 27, August 29 and September 29, 1960. On the first visit, she felt remarkably well. The spleen was not palpable but pin-point petechiae were noted on both arms. The Rumpel-Leede test was negative, the bleeding time was normal, the platelet count was 253,000 per c.mm. and the prothrombin time was 100%. The hemoglobin level was 13.7 g. %, and the corrected sedimentation rate was still elevated at 38 mm. in one hour. A blood culture was reported negative. On July 27, the corrected sedimentation rate was 23 mm. in one hour and the serum protein electrophoresis revealed a slight abnormality: a gamma globulin value of 18.8% (normal: 14 to 16%). On September 29, the corrected sedimentation rate was still slightly elevated, at 21 mm. in one hour. Three months after cessation of treatment, she had gained 10 lb. and had resumed her normal activities. The pin-point purpura, a finding which had never been noticed before this recent illness, persisted and remained unexplained.

RESULTS

Two patients, both treated by phenethicillin only, were definitely cured. A third patient (Case 2) had a bacterial cure but died of massive cerebral hemorrhage, pulmonary edema and acute nephrosis. In all cases, splenomegaly persisted for several weeks in spite of definite improvement as judged by the normal temperature, the sensation of well-being and negative blood cultures. Similarly, the sedimentation rate in all patients remained elevated for a variable period of time after cessation of the drug. In one patient (Case 1), it became normal two months after therapy, and in the other it was still slightly elevated three months later. A persistently elevated sedimentation rate during successful treatment and for periods of one to two months after cessation of treatment has previously been observed by Geraci.[9]

The phenethicillin blood levels were satisfactory in all three patients. The average range one hour after the ingestion of the drug was from 6.8 μg./ml. to 10.3 μg./ml. (Fig. 1).

The drug was well tolerated, although minor side reactions were observed. Two patients had nausea and diarrhea during the first week of therapy. Anal pruritus was noted by one. No toxicity was recognized clinically or by screening laboratory tests of the hemopoietic, hepatic and renal systems.

DISCUSSION

This is the authors' first experience with oral therapy of bacterial endocarditis.[10] The oral route appears desirable for the patient's comfort and eliminates complications resulting from frequent intramuscular injections. The treatment begun in the hospital, if satisfactory, may be continued at home and thereby may shorten considerably the period of hospitalization. As mentioned previously, others[1-5] have found that oral penicillin V and streptomycin were satisfactory in cases of subacute bacterial endocarditis caused by sensitive organisms.

Recent comparative studies[6-8] have shown that phenethicillin potassium produces higher serum concentrations than penicillin V. Others[11-12] believe that in spite of this the bacterial activity may not be increased. Nevertheless, it appears from this preliminary study that oral phenethicillin may provide adequate therapy for bacterial endocarditis. A smaller amount of phenethicillin than that given in the cases reported, such as 500 mg. every three hours during the daytime, particularly if associated with probenecid administration, may be as satis-

factory, but this remains to be proved. It is also still considered wise to administer streptomycin concurrently in most cases for at least seven to 15 days.

SUMMARY

Three cases of bacterial endocarditis successfully treated by administration of oral phenethicillin potassium are reported. The drug was relatively well tolerated and the absorption, as demonstrated by serum concentrations, was satisfactory.

We acknowledge, with appreciation, the constructive comments of Dr. Paul David, Director of the Institute of Cardiology. We would also like to thank Drs. O. Gialloreto and Y. Desrochers of the Institute of Cardiology for having referred these patients to us; Drs. H. S. Root and D. A. Howell of the Montreal General Hospital, for the autopsy report in Case 2; and Dr. E. M. E. Morigi (Syracuse, N.Y.) and Mr. B. R. de Massy (Montreal) of the Bristol Laboratories.

ADDENDUM

Both surviving patients are still well six months after cessation of therapy. Since the writing of this paper, another case, caused by *Streptococcus faecalis* inhibited by 0.78 μg./ml. of phenethicillin, was successfully treated by this antibiotic in combination with streptomycin. The serum bactericidal activity was 1:8 and the serum level was 7.7 μg./ml. one hour after 1 g. of phenethicillin. This patient is also well three months after treatment.

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RÉSUMÉ

Les auteurs présentent trois cas d'endocardite bactérienne traités avec succès la phénéthicilline orale, nouvelle Pénicilline semi-synthétique. Une légère intolérance gastro-intestinale a été observée chez deux malades mais aucun effect toxique ne fut noté. Les niveaux sanguins démontrent une absorption satisfaisante. Cette étude préliminaire suggère que cette nouvelle Pénicilline orale est efficace dans le traitement de l'endocardite bactérienne lorsque l'organisme en cause lui est sensible.

THE VALUE OF CHEST RADIOGRAPHS ON ADMISSION TO GENERAL HOSPITALS*

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ROUTINE CHEST radiographic examinations in industry and of office workers, students, teachers, food handlers, etc. have proved their value for the last 20 years. However, it should be pointed out that the greatest drawback of this type of survey is the fact that only a certain percentage of the general population can be reached. The unemployed or an employee in a small business enterprise will usually not have this benefit unless he asks for it personally. Furthermore, the older generation will drop out of this survey for various reasons. Many office or industrial workers, for instance, may become independent and start a small business at a later age: a garage worker may have his own service station, a detail man of a pharmaceutical firm may open a drug store, etc. In other words, the routine chest radiographs taken by voluntary organizations will include an age group from 16 years to 45 years with a peak load at 20-35 years.

If one thinks only in terms of pulmonary tuberculosis — and this was, after all, the primary reason for these surveys — the surveys achieve their objective. The picture, however, is different if we consider other diseases of the chest as well.

Fig. 1 shows, by the dotted line, the mortality rate of pulmonary tuberculosis in Canada from 1931 to 1958. While this mortality was in the neighbourhood of 59 per 100,000 living in 1931, it dropped consistently over the years, with slight spikes during the war years, and is now down to about four per 100,000 living. On the other hand, the solid line, which represents the mortality from lung cancer, shows a steady, although slow, rise of mortality. In 1952-53 the two curves intersected and, in 1958, the lung cancer mortality rate was over four times as much as that for tuberculosis. If separate curves are drawn for males and females, the mortality for males would be up in the high forties. This mortality varies widely in the different provinces of Canada. The question now is "What means do we have available in order to reach the older population?" Naturally, routine chest radiographic examinations of every person in Canada would be the ideal answer, but this is practically impossible, especially if it is done on a yearly basis. One could, however, approach this ideal

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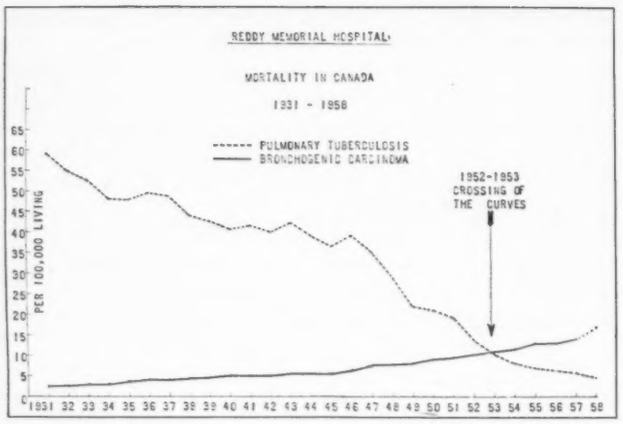

Fig. 1

somewhat by qualified selection. Routine chest radiographs on every hospital admission, and perhaps even on outdoor clinic patients, might be of value.

In 1946, the Reddy Memorial Hospital in Montreal started such a survey as a pilot study, the first hospital in Canada to do so. The results within less than a year were so encouraging that this study was converted into a compulsory arrangement. Now, after 14 years, one should be able to see whether these initial results persisted and whether it was worth while to continue with this system.

Fig. 2 shows the average age curve for all patients based on over 75,000 admissions, after deducting infants, births in hospital and maternity cases. During the 14 years some changes in the selection of cases were made for practical reasons. For instance, it would have been a duplication if routine chest radiographs were taken on patients who were only recently discharged from the hospital and were re-admitted within less than six weeks. Or, if the patient could show evidence that he had had a negative routine chest radiograph within a reasonable time before admission — including those taken in miniature mass surveys — further examination was not insisted upon unless the patient was admitted for a disease referring to the chest. Maternity cases had a radiograph taken first at admission. However, it was soon found that some patients had contracted tuberculosis or other chest diseases during the prenatal period and, when they were admitted for delivery, there was no time to pay primary attention to the chest lesion. Therefore, radiographs were taken, as in most prenatal clinics, as soon as the patient was seen for the first time during her prenatal care. This applied to private as well as to clinic patients. The ideal procedure would have been to have the patient undergo radiography again on admission, because some disease could have developed after the initial radiograph. This could not be carried out routinely, firstly, on account of the double cost involved and, secondly, because of the reluctance on the part of the patient as well as of many obstetricians who feel that radiographic examinations may be harmful to the fetus. However, for every radiograph of the abdomen taken to make a diagnosis of twins or for the position of the fetus or pelvimetry, it would require the taking of many full-size chest radiographs to equal the amount of radiation to the fetus. X-ray examination for obstetrical reasons exposes the fetus directly to radiation, whereas the fetus is fairly well protected when a chest roentgenogram is taken with proper equipment. Even then one could not use the maternity statistics, because patients who showed disease, especially

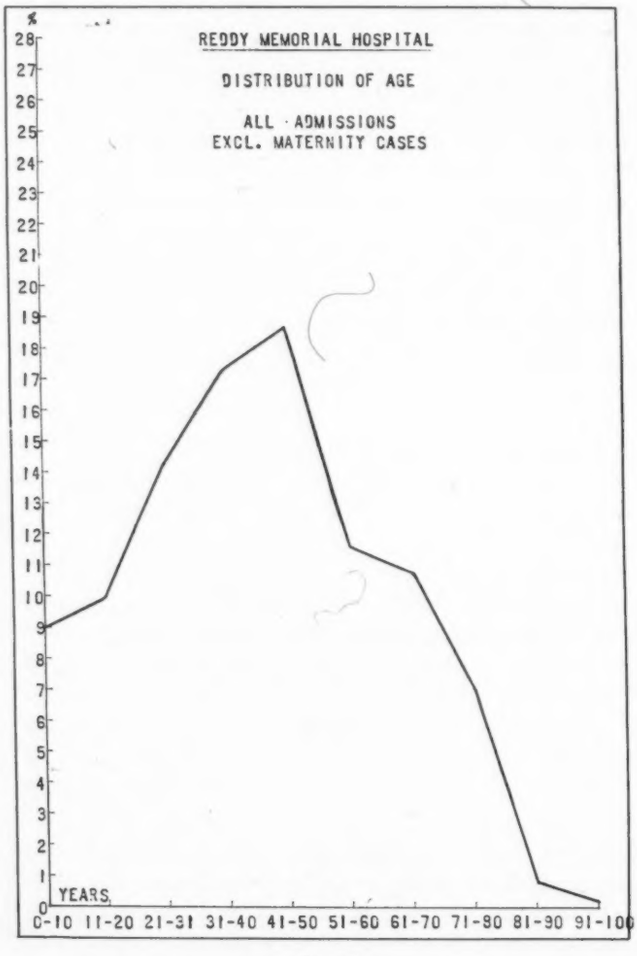

Fig. 2

tuberculosis, during pregnancy would not have been admitted to this general hospital but diverted to other institutions. Statistics would become noticeably incorrect due to this preselection.

Results of the Survey

Table I shows the breakdown of all admissions. From 1946 to 1959 there were about 79,000 admissions, which are reduced to 41,000 by elimination of the categories just mentioned.

Table II gives the breakdown of those cases which were used in the survey. It is surprising to note that 4.5% of these had an abnormal chest radiograph. As seen from Table III, two-thirds of

TABLE I.—REDDY MEMORIAL HOSPITAL

Total admissions 1946 - 1959			79,353
Less	Readmissions and admissions with recent chest x-rays	1,290	
	Maternity cases	18,187	
	Births in hospital	18,319	
Subtotal			37,896
Cases used for survey			41,457

these had unsuspected disease. Patients were admitted to the hospital for treatment of diseases not related to the chest, such as accidents, uterine disease, hernia, or duodenal ulcers, for example.

TABLE II.—REDDY MEMORIAL HOSPITAL

Routine chest x-rays	*Survey 1946 - 1959*	
Normal findings	39,592 cases	95.5%
Abnormal findings	1,865 cases	4.5%
Total	41,457 cases	100%

Table IV shows a breakdown of these 1276 abnormal, unsuspected radiographic findings. The proportion of cases of active pulmonary tuberculosis was only 10%, while those with malignant

TABLE III.—REDDY MEMORIAL HOSPITAL
ABNORMAL FINDINGS

Known disease	589 cases	31.6%
Unsuspected disease	1276 cases	68.4%
Total	1865 cases	100.0%

tumours constituted 12.5%. The "miscellaneous" group includes such conditions as mycotic disease of the lung, benign tumours, foreign bodies, diaphragmatic hernia, and the like. The term "Undiagnosed" indicates that it was not possible to explain the radiological findings during the patient's stay at the hospital.

TABLE IV.—REDDY MEMORIAL HOSPITAL
1276 UNSUSPECTED CASES

Cardiovascular disease	351 cases	27.5%
Pneumonitis and lung abscess	96 "	7.5%
Pulmonary tuberculosis, active	128 "	10.0%
Chronic pulmonary conditions	352 "	27.5%
Tumours, malignant	159 "	12.5%
Miscellaneous	127 "	10.0%
Undiagnosed	63 "	5.0%

Table V indicates the management of these patients. The first line shows the chest conditions which had precedence over the original disease for which the patient was admitted. These were 415 in number, about one-third of all those with unsuspected chest disease. In the second line, the original disease was an emergency and, therefore, had precedence over even important chest disorders; these constituted 40% of all those with abnormal chest radiographs. In the last line are listed those in

TABLE V.—REDDY MEMORIAL HOSPITAL—MANAGEMENT OF PATIENTS
1276 UNSUSPECTED CHEST CONDITIONS (ALL CASES)

Chest condition precedence over original disease	415 cases	32.5%
Original disease emergency, precedence over important chest condition	510 cases	40.0%
Original disease treated. Chest condition chronic and/or not requiring treatment	351 cases	27.5%

whom the chest condition was chronic and/or did not require treatment, while the original disease for which the patient was admitted was treated. There were 315 such cases, or 27.5%.

TABLE VI.—REDDY MEMORIAL HOSPITAL—MANAGEMENT OF PATIENTS (SURGICAL CASES ONLY)
957 CASES = 75% OF ALL CASES

Operation for original disease cancelled or deferred on account of chest condition	352 cases	36.7%
Operation for original disease performed, knowledge of chest condition important to surgeon and anesthetist	478 cases	50.0%
Chest condition chronic and unimportant	127 cases	13.3%

Table VI deals only with surgical conditions. Of these patients with unsuspected chest disorders 957, or 75%, were surgical cases. In more than one-third, the operation for the original disease for which the patient was admitted to hospital was cancelled or deferred because of the chest condition. In one-half of the cases, the operation for the original disease had to be performed, but knowledge of the chest condition was of utmost importance for the surgeon as well as for the anesthetist. The cases in which the chest condition was chronic and important amounted to only 13.3%, almost a negligible figure.

The following data illustrate features of interest in certain individual cases.

The patient whose chest radiograph is depicted in Fig. 3 was admitted for a recurrent inguinal hernia. This film showed an aneurysm of the thoracic aorta of considerable proportions.

Fig. 4 shows the film of a patient who was admitted for repair of a postoperative hernia. He had been operated on for chronic gallbladder disease and appendicitis in another hospital two months previously. No roentgenogram of the chest was taken at that time. The routine chest film revealed a shadow in the right lower lung field. The incisional hernia was not repaired but a pneumonectomy revealed a bronchogenic carcinoma. This tumour must have been present at the time of his previous admission, and if a chest radiograph had been taken in that hospital, his pneumonectomy would have been carried out that much earlier.

The patient whose chest radiograph is illustrated in Fig. 5 was admitted with a fracture of the neck of the femur. A roentgenogram of the chest showed a pulmonary cyst.

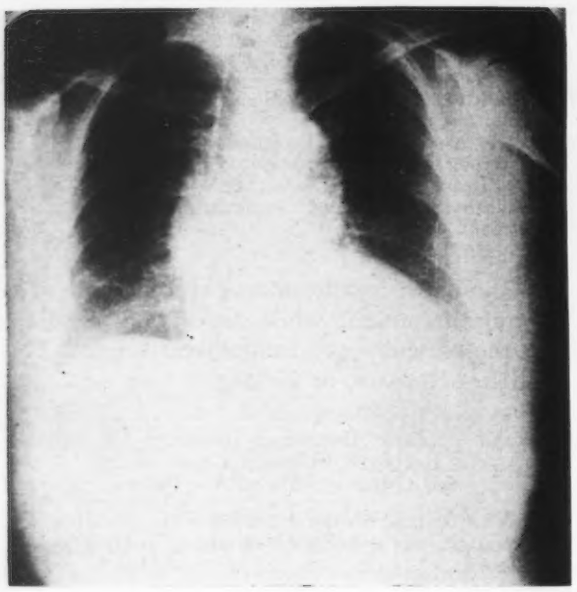

Fig. 3

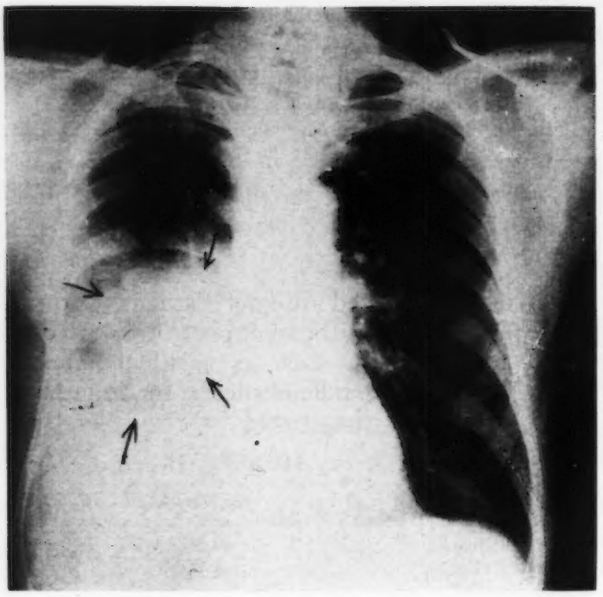

Fig. 4

A patient was admitted for hemorrhoids, without any lung symptoms whatsoever. A radiograph of the chest clearly showed the presence of a lung abscess (Fig. 6). Hemorrhoidectomy was deferred.

A patient was admitted to hospital to undergo an operation for bunions. Chest radiograph showed wide-spread silicosis (Fig. 7).

A patient was admitted for gallbladder disease but the radiologist noted that the right breast was higher than the left (Fig. 8). He attributed this to a possible malignancy in the right breast. Clinical examination subsequently revealed a tumour in the right breast which had not been noticed before. Radical mastectomy confirmed the diagnosis of carcinoma.

A patient was admitted, under arrangement with the Workmen's Compensation Commission, because of an injury to the left lower side of his chest, and a rib fracture was suspected. Radiographs of the ribs did not show any lesions. If a routine chest radiograph had not been taken at the same time, the lesion in the apex on the opposite side would have been overlooked. It proved to be a tuberculoma.

Fig. 10 is not an error of the technician. The patient has situs inversus: the stomach and heart are on the right and the liver shadow on the left side. This patient was admitted for a gynecological disease. Further investigation showed that the situs inversus was complete. It did not make any differ-

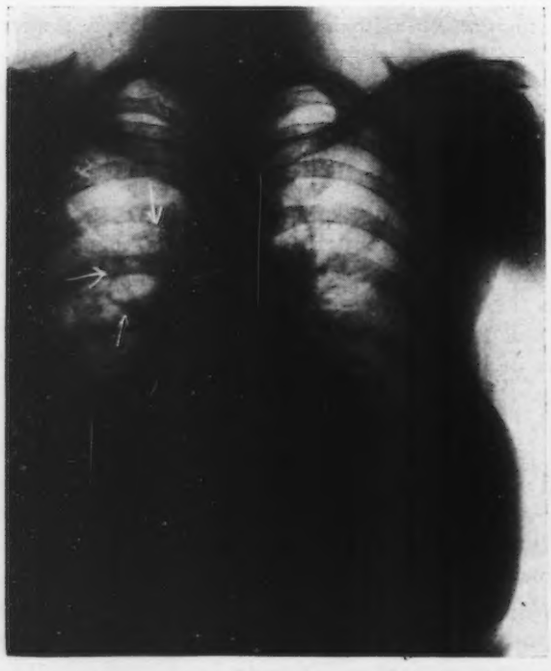

Fig. 5

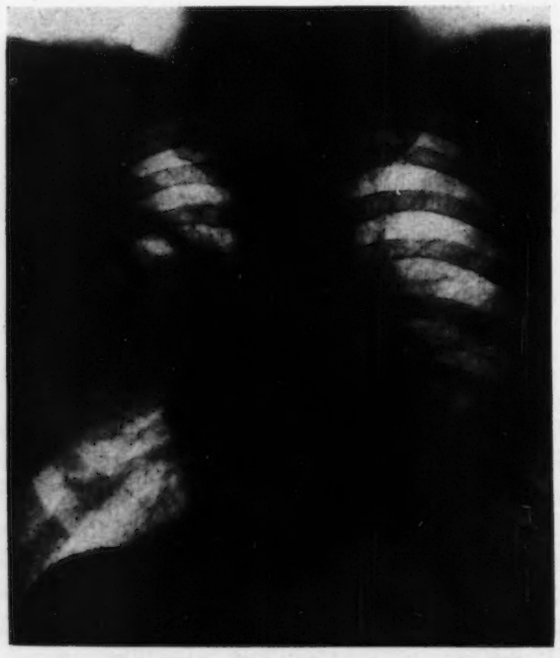

Fig. 6

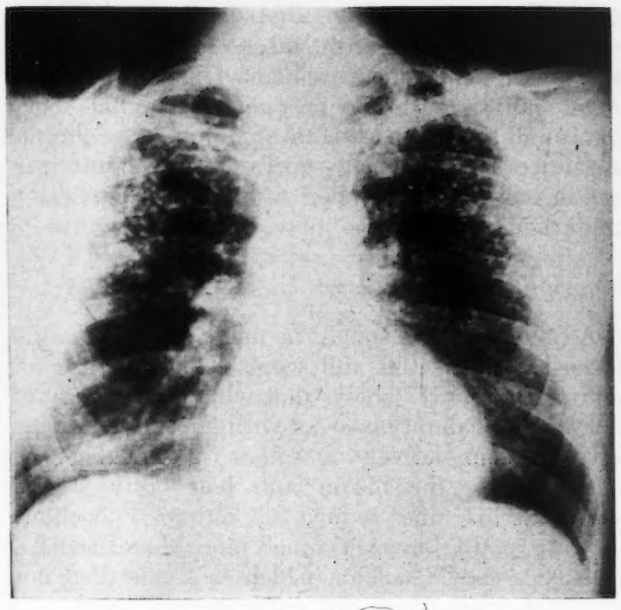

Fig. 7

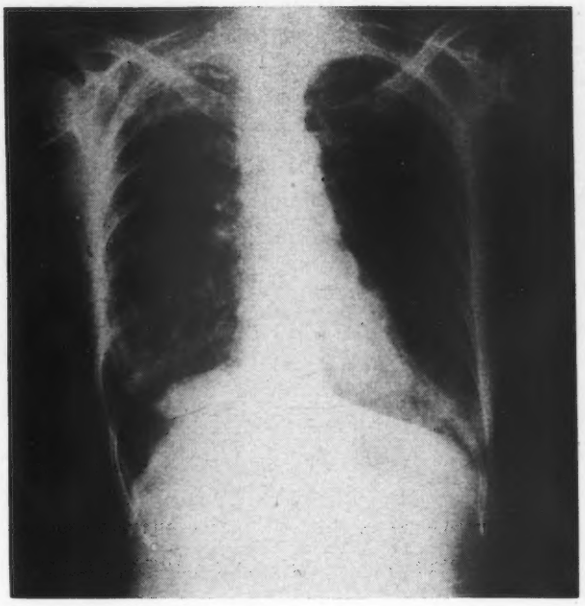

Fig. 8

ence to the gynecologist whether the left ovary was on the right side and the right one on the left; however, things would have been different had the patient suffered from appendicitis or cholecystitis.

A compulsory routine chest radiograph arrangement for every patient admitted to hospital is only as effective as its weakest link. In other words, the co-operation of the entire hospital staff is required. It does not help if the radiologist discovers a lesion in a routine chest radiograph and the clinician does not pay attention to the finding or, if by some lack of administrative liaison, the findings do not come to his attention. Fig. 11a illustrates such an example: this woman was admitted in 1955 for a gynecological procedure, which was carried out. There is a bulging shadow of the right border of the heart silhouette. At that time, the radiologist thought of a possible pericardial cyst, but, in order to investigate this shadow further, he asked for lateral films and barium meal series (Fig. 11b). The radiologist made a final diagnosis of a well-circumscribed shadow lying posteriorly within the substance of the lung, most likely a tuberculoma. The next radiograph was taken two years later and did not show any changes. Fig. 11c shows the lesion five years later. The circumscribed shadow had disappeared but the lesion had broken through into a bronchus and the patient had recently been subjected to resection of the middle and lower lobes for active pulmonary tuberculosis. This example shows what

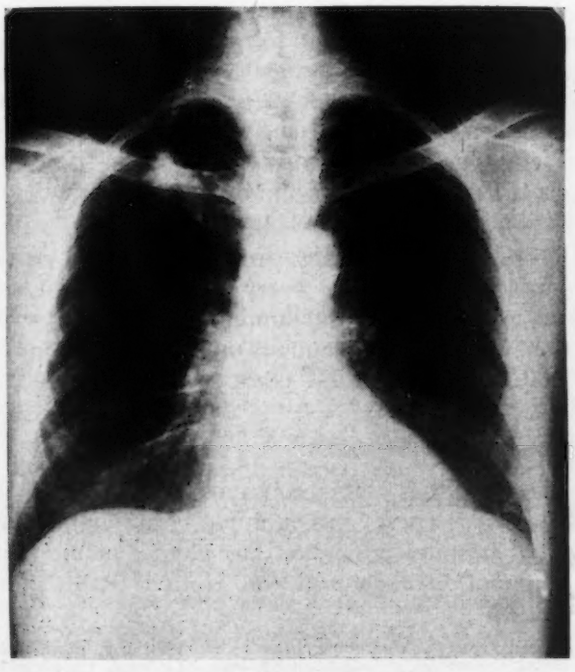

Fig. 9

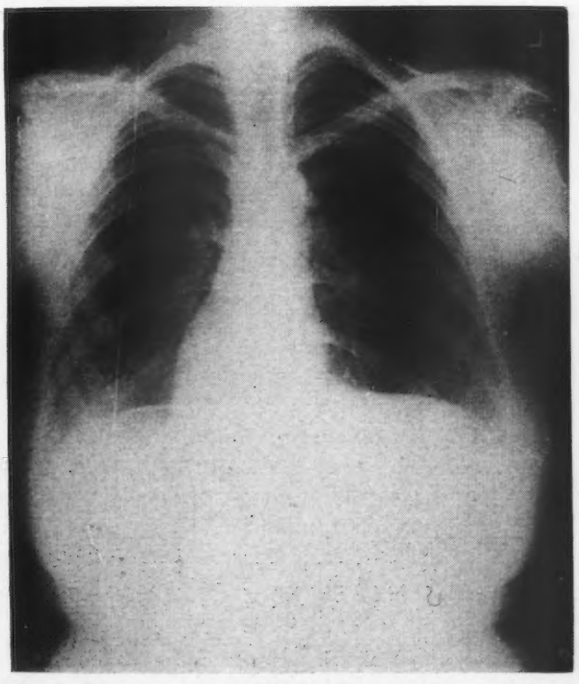

Fig. 10

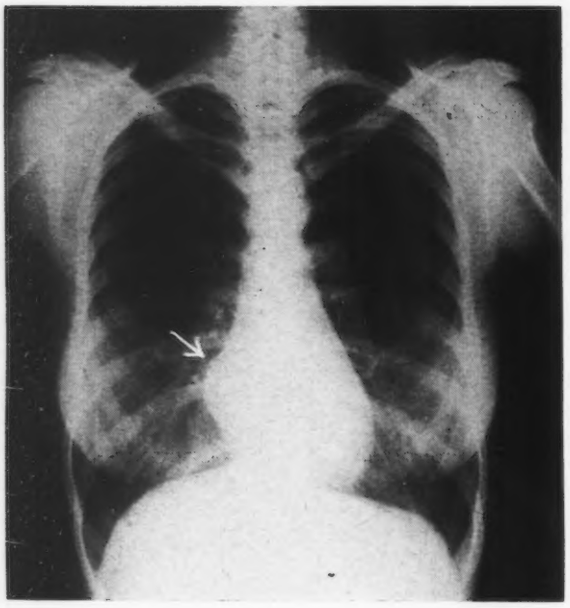

Fig. 11a

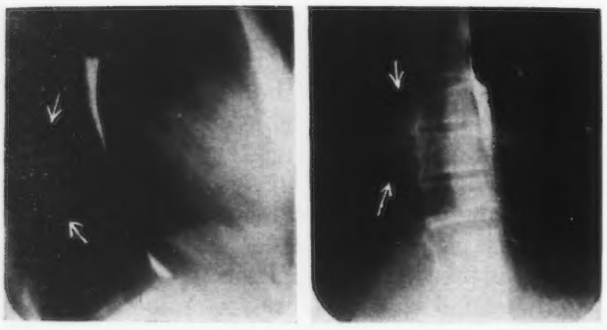

Fig. 11b

can happen if patients with these lesions are not followed up properly. It also adds substantially to the plea that every coin lesion over 1 cm. in diameter should be removed as soon as possible, and that one should abandon the "wait and see" attitude.

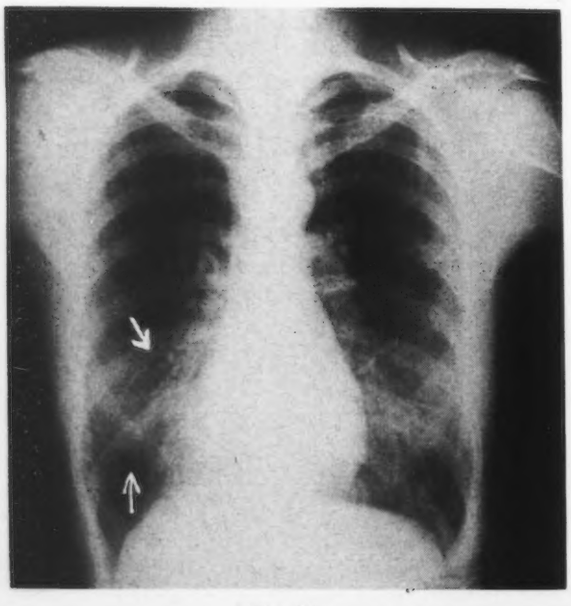

Fig. 11c

It may be pointed out that the greater number of the 159 patients with unsuspected malignancy, mostly bronchogenic carcinoma, came to hospital for repair of a simple or recurrent hernia. They almost all had the additional symptom of a "chronic cigarette cough" which received its real interpretation only when the chest radiograph showed the underlying cause.

RADIATION HAZARDS

A few comments should be made about radiation hazard, because this still seems to be a cause for alarm. Table VII* shows that while fluoroscopy of one minute's duration—even with good protection—involves cumulatively a rather high dosage of gamma rays, the mirror and lens optic of the miniature machines reduce this radiation considerably. It is still, however, much more than that of a full-size 14 x 17 in. film, which as a rule does not use more than 0.1 to 0.3 milliroentgen (mr).

TABLE VII.—COMPARATIVE RADIATION HAZARDS BY P.A. CHEST X-RAY EXAMINATION

(Adapted from L. Henry Garland, San Francisco, Calif., and others)

Method of examination	*Gonadal dose*	*Skin dose*	*Bone marrow dose*
Film 14"x17"..	0.3 - 1.2 mr	60 mr	6 - 12 mr
Minifilm lens or mirror optic.....	10 - 40 mr	600 mr	60 - 120 mr
Fluoroscopy: 1 minute			
Adults....	20 - 100 mr	30 r	
Infants....	20 r		

GONADAL DOSE

From natural sources—average per year.....	100 mr.
From luminous watch dial—average per year....	100 mr.

The danger of radiation does not lie with chest radiographs or with the miniature radiographs, but most frequently is due to physicians who have fluoroscopic x-ray equipment but do not have the time to adapt their eyes properly. Therefore, they use high milliamperage and longer exposure time. Certainly, chest fluoroscopy should be restricted to short and definite procedures such as pulmonary function studies or bronchography.

Every person receives, from the general background, about 100 mr every year and about the same amount from the luminous dial of a wrist watch. To equal this amount one could be exposed to 100 to 1000 14" x 17" chest radiographs.

CONCLUDING REMARKS

It seems that the acceptance of the value of compulsory chest radiographic examination in general hospital admission has gained momentum throughout Canada and the United States. The

*Adapted from L. Henry Garland et al., San Francisco, *The Hospital Counsellor*, American College of Chest Physicians, No. 10, December 1957.

figures shown here support the contention that the effort of these examinations is rewarded by earlier diagnosis of chest disease, especially of bronchogenic carcinoma. However, there are still a number of hospitals, especially private ones, which have not yet adopted this system. At the Fifth International Congress on Diseases of the Chest, held in Tokyo in 1958, a special committee, of which one of us (W.E.K.) was a member, forwarded a resolution for general adoption of this procedure. We should like to go one step further. Once the means are available, this examination should be carried out in all outpatient departments, at least on a selective basis—for example, all males over 40 years—even if the patient comes in for only a cut finger. By this method the early diagnosis of bronchogenic carcinoma and other chest diseases will be furthered.

The authors wish to express their appreciation to two former radiologists of the Reddy Memorial Hospital, Dr. E. Crutchlow, who instituted the compulsory scheme, and his successor, Dr. J. P. Jean, without whose accurate records this study could not have been carried out; and to thank their chief technician, Miss Jill Harlow, and her staff for their great assistance in collecting and computing all statistical data.

SPECIAL ARTICLE

SOME APPLICATIONS OF STATISTICS TO MEDICAL RESEARCH

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PART III OF FOUR PARTS

CHI SQUARE TEST

AN investigator frequently has a hypothesis about the population ratio and measures the characteristics of the small sample in an attempt to refute or substantiate his hypothesis. The chi square test goodness of fit enables one to determine if there is a significant difference between expected theoretical ratios and those obtained by experiment. Great use is made of it by geneticists and plant and animal scientists where the familiar 3 : 1 and 9 : 3 : 3 : 1 ratios are frequently applied.

The chi square test goodness of fit was developed by Karl Pearson in 1899. It involves the calculation of the deviation of the theoretical from the observed data. This is then compared with a χ^2* table which shows the frequency of occurrence of a deviation of this magnitude in repeated random sampling of the theoretical population. When the χ^2 value is small, the observed deviation is likely due to sampling error, whereas if it is large the deviation is probably due to a misleading theoretical ratio. The test involves the assumption of a null hypothesis, which is that there is no real difference between the observed and the theoretical data. The test is performed in the following fashion: The deviations between pairs of observed and theoretical values are squared, divided by the theoretical values, and the results added.

The formula is: $\chi^2 = \Sigma \frac{(O - T)^2}{T}$

O = observed value.
T = theoretical value.

Example: An investigator is studying the sex ratio of patent ductus arteriosus. There is no apparent reason why the disease should not appear with equal frequency in males and females. Of 100 affected patients the investigator finds that 67 of them are female and 33 are male. Is this ratio sufficiently different from the expected theoretical ratio of 50 : 50 to warrant the conclusion that factors other than chance are the reason for the preponderance of females?

	Theoretical	*Observed*	$O - T$	$(O - T)^2$	$\frac{(O - T)^2}{T}$
Male	50	33	−17	289	$\frac{289}{50} = 5.78$
Female	50	67	+17	289	$\frac{289}{50} = 5.78$

$$\chi^2 = \Sigma \frac{(O - T)^2}{T} = 11.56$$

The number of degrees of freedom is equal to one less than the number of classes of data. Here there are two classes, male and female, hence one degree of freedom. In Goulden's text (page 444)[4] is found a χ^2 table. Probability is across the top and degrees of freedom are down the left-hand side. The χ^2 values for 5%, 1% and 0.1% probability and one degree of freedom are 3.84, 6.64 and 10.83 respectively. The calculated χ^2 value was 11.56. The interpretation of these results is that in less than 0.1% of cases (1 in 1000) would a deviation as large as 67 : 33 from the theoretical of 50 : 50 be expected to occur due to chance alone. It is therefore very likely that factors

*χ is the Greek letter chi.

other than chance, e.g. endocrine, heredity, etc., are responsible for this deviation from the theoretical.

More than two classes or ratios other than 1 : 1 may be compared as follows: Suppose that the relative frequencies of A B O blood groups are being investigated in an isolated community of apparent Chinese origin. On this assumption the expected ratio would be 31% O : 25% A : 34% B : 10% AB. From random selection of 100 people the following ratios were found: 0–37, A–20, B–30, AB–13. Is this ratio sufficiently similar to the expected to suggest that any observed difference is due to sampling error or does it indicate that the original hypothesis is misleading?

We proceed as follows:

	Theoretical	*Observed*	$O - T$	$(O - T)^2$	$\frac{(O - T)^2}{T}$
O	31	37	+6	36	$\frac{36}{31} = 1.16$
A	25	20	−5	25	$\frac{25}{25} = 1.00$
B	34	30	−4	16	$\frac{16}{34} = 0.47$
AB	10	13	+3	9	$\frac{9}{10} = 0.90$
			0		

$$\chi^2 = \Sigma \frac{(O - T)^2}{T} = 3.53$$

Degrees of freedom = 4 − 1 = 3

p at 5% and 1% for 3 D.F. is 7.82 and 11.34 respectively. For 3 D.F. and a χ^2 value of 3.53, p is about 30%. Therefore the difference between the observed and theoretical data would be expected to occur due to chance in about 30% of cases. The null hypothesis that there is no real difference between the observed and the theoretical data is upheld. Any observed difference is most likely due to sampling error.

Whenever the investigator gets a high χ^2 value he may ask himself two questions:

(1) Is this an unusual sample of the hypothetical population ratio?

(2) Does the hypothesis represent the true population ratio?

This is something which the χ^2 test cannot decide. Instead it indicates the probability that the observed ratio is no different from the expected. High χ^2 values suggest that the observed ratio is an unlikely one under the conditions of the hypothesis.

The χ^2 frequency distribution is not normally distributed but heavily skewed towards the smaller values. This is due to the fact that small deviations resulting from sampling error are much more likely to occur than are large ones. The χ^2 frequency distribution has a lower limit of zero and an upper one of infinity. When the number of classes is two and the value in one of the classes is small (less than five), there is a bias arising from the discontinuity of the observed χ^2 distribution, which leads to the calculation of a χ^2 value which is too large. Yates' correction for continuity, namely the subtraction of 0.50 from each O–T value before squaring, nearly eliminates this bias. If there are more than two classes and the value in any of the classes is less than five, it should be combined with one of the other classes and the degrees of freedom adjusted accordingly.

χ^2 FOR INDEPENDENCE

Suppose that the relationship between the dose of a drug given and the clinical response is being investigated. The clinical response is graded as follows: A—much improvement, B—moderate improvement, C—no change or deterioration of condition. The drug is administered in three different levels, 1, 2 and 3, to 100 people. At the end of a specified time interval the patients are assessed as to the effect of the drug. The results are as follows:

	A	*B*	*C*	
Level 1	4	13	19	36
Level 2	10	19	9	38
Level 3	14	8	4	26
	28	40	32	100

The null hypothesis is that therapeutic response and the level of drug administered are independent of one another. If this is so, then the response of 36 people on level 1 of the drug should not differ from that of level 2 or 3. The people on each level of drug should be divided as to clinical response in the same ratio as is given by the whole group. Thus the subtotals are the basis for calculating the theoretical values, i.e. level 1, group A—the theoretical value is 28 (the total of group A) times 36 (the total of level 1) divided by 100 (the total number of patients). Calculation of other theoretical values is shown in the following:

Group A

	Observed	*Theoretical*
Level 1	4	$\frac{28 \times 36}{100} = 10.08$
Level 2	10	$\frac{28 \times 38}{100} = 10.64$
Level 3	14	$\frac{28 \times 26}{100} = 7.28$
	28	

Group B

	Observed	*Theoretical*
Level 1	13	$\frac{40 \times 36}{100} = 14.40$
Level 2	19	$\frac{40 \times 38}{100} = 15.20$
Level 3	8	$\frac{40 \times 26}{100} = 10.40$
	40	

Group C

	Observed	*Theoretical*
Level 1	19	$\frac{32 \times 36}{100} = 11.52$
Level 2	9	$\frac{32 \times 38}{100} = 12.16$
Level 3	4	$\frac{32 \times 26}{100} = 8.32$
	32	

	Level 1	Level 2	Level 3
Total (100)	36	38	26

The χ^2 test is performed as follows:

Group A

	$O - T$	$(O - T)^2$	$\frac{(O - T)^2}{T}$
Level 1	−6.08	36.97	3.67
Level 2	−0.64	0.41	0.04
Level 3	+6.72	45.16	6.20
			9.91

Group B

	$O - T$	$(O - T)^2$	$\frac{(O - T)^2}{T}$
Level 1	−1.40	1.96	0.14
Level 2	+3.80	14.44	0.95
Level 3	−2.40	5.76	0.55
			1.64

Group C

	$O - T$	$(O - T)^2$	$\frac{(O - T)^2}{T}$
Level 1	+7.48	55.95	5.06
Level 2	−3.16	9.99	0.82
Level 3	−4.32	18.66	2.24
			8.12

$$\Sigma \frac{(O - T)^2}{T} = 9.91 + 1.64 + 8.12 = 19.67$$

$$\begin{aligned}\text{Degrees of freedom} &= (\text{columns} - 1)(\text{rows} - 1) \\ &= (3 - 1)(3 - 1) \\ &= 2 \times 2 = 4\end{aligned}$$

For 4 D.F. the χ^2 values at 5%, 1% and 0.1% are 9.49, 13.28 and 18.46 respectively. The null hypothesis, that therapeutic response is independent of dose administered, is refuted. The probability that the increased therapeutic response from the increased dosage administered is due to chance is less than 1 in 1000. Therapeutic response is highly dependent upon dosage of drug administered.

SUMMARY

The chi square test goodness of fit and chi square for independence enable one to compare theoretical expected ratios with those obtained by experiment. The methods of performing the tests are explained and examples of each are given.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

HOSPITAL TROUBLES IN HALIFAX

From time to time there have been indications that all was not going smoothly in the Victoria General Hospital in Halifax. Into the long history of all these troubles it is not our intention, at present, to enter, but we may note that for several years the hospital has been administered directly by the government of Nova Scotia, which is responsible for its maintenance, and that one of the charges of its critics is that party politics figure too largely in the management of the hospital and in the consideration of appointments. We must also admit that there seems to be some incompatibility of ideas, if not of temper, among the staff. The government has recently appointed a commission to administer the affairs of the hospital, and sincere hopes are entertained that a new era is dawning for this important institution, and that it may soon command, even more than it has done, the trust and support of the profession and public throughout the province. Considering all the circumstances of the case, the previous history of the hospital, the numerous interests, frequently conflicting, which are involved, the atmosphere of party politics that has been made to surround the hospital, local prejudices and professional animosities, the commission has no easy task before it. The personnel, however, of the commission commands the respect and confidence of the whole community, and we believe each member is animated by a sincere desire to devise such improvements in general management and such a scheme of medical organization as shall place the hospital in a position to fulfill all the functions of a first-class institution.

A hospital has three functions. The first is generally recognized,—it is a place for the treatment of sick and injured people. Secondly, it is the place where properly educated persons are trained to study and treat disease. This is its educative function. It is the technical school of medicine. In the third place, it has a scientific function. It must contribute to the general store of knowledge. It is the great laboratory of medical science. No hospital, at least no public hospital, is doing all its duty unless it serves these three purposes. To secure such results in a hospital service, a thorough organization of its medical staff is demanded. In each department, medical, surgical, and, if the hospital be a large one, in the various special departments, there should be a chief visiting officer with an assistant, or senior and junior assistants, and a resident medical officer.—Excerpt from an editorial, *Canadian Medical Association Journal*, 1: 254, March 1911.

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CASE REPORTS

LOCALIZED PSEUDOANTHRAX

J. D. YEO, M.B., B.S., *Gainsborough, Sask.*

G.H., A 54-YEAR-OLD farmer, was first seen on July 1, 1960, complaining of a small lump on the dorsum of the right hand at the base of the forefinger. He had first noted this swelling one week previously and said that it had been slowly increasing in size since that time. It had not discharged any material and was only occasionally tender. The patient's health was unimpaired and his past history was irrelevant. There had been no history of trauma to the hand, and he had never experienced similar lesions elsewhere. In his farm work he had a history of contact with domestic animals, particularly cows, but all of his cattle were apparently healthy and had recently been screened by a veterinary surgeon.

Examination revealed a non-tender cystic swelling, 1 cm. in diameter at its base and 2 mm. in depth, with a surrounding indurated border remarkably free of erythema. The cyst was dark brownish in colour owing to the underlying serosanguineous cystic fluid, which was aspirated with care. Despite the absence of signs of acute inflammation, an isolated, enlarged, slightly tender lymph node was palpable in the right axilla. The patient was afebrile and appeared in good health. The remainder of his physical examination revealed no abnormal findings.

As a diagnosis of localized anthrax could not be excluded, the fluid aspirated from the cystic swelling was sent for bacteriological examination and the patient was isolated in hospital and treated with chloramphenicol.

A preliminary bacteriological report received on July 7, 1960, indicated that culture of the fluid from the lesion was growing an organism which was either *B. cereus* or *B. megaterium* (the latter is also known as *B. anthracoides* or *B. pseudoanthracis*). Since both of these organisms are generally regarded as non-pathogenic to humans, chloramphenicol was discontinued and the patient was discharged from hospital, his local lesion and clinical condition unchanged.

He was kept under observation for the next month, during which time the lesion gradually disappeared without discharge, slough or scar, and the axillary lymph node was no longer enlarged, tender or palpable.

Final bacteriological differentiation of the organism was carried out at the Laboratory of Hygiene, Ottawa, where it was identified as *B. megaterium*.

DISCUSSION

B. megaterium (*B. anthracoides; B. pseudoanthracis*) forms a powerful hemolysin, most active against the red blood cells of man, monkey and the guinea-pig. The presence of oxygen is necessary for its production. When it is injected subcutaneously in guinea-pigs, it gives rise to a large local swelling with subsequent necrosis. Intravenous or intraperitoneal injection in guinea-pigs results in hemoglobinuria but does not cause death except when given in large doses, approximately 10 c.c. or more. According to Warden, Connel and Holly, this hemolysin is identical with the lethal toxin which this organism is capable of producing and which results in abdominal distension, hemolysis, sanguineous transudation into the intestine and exsanguination into the peritoneal and pleural cavities and interstitial tissues of the thighs.

In humans, lesions due to *B. megaterium* are rare, and the organism is usually regarded as non-pathogenic to man. Its main clinical significance lies in the importance of differentiating it from *B. anthracis*. Nevertheless, as in the case of other organisms regarded as non-pathogenic, it is possible that *B. megaterium* may acquire enhanced virulence and assume pathogenic potentialities for man, just as, in rare instances, *B. subtilis* may cause fatal septicemia and *B. cereus* may produce a lethal toxin in starchy food that is capable of causing major outbreaks of food poisoning.

SUMMARY

A case of localized pseudoanthrax due to infection by *B. megaterium* (*B. anthracoides*: *B. pseudoanthracis*) was observed in a 54-year-old farmer.

This infection was manifested clinically as a superficial bullous lesion, 1 cm. in diameter, located on the dorsum of the hand at the base of the index finger. A single, enlarged, slightly tender axillary lymph node was palpable on the side of the lesion. The patient was not systemically ill and the local lesion and lymphadenopathy subsided completely in four to five weeks with no discharge, slough or scar.

This case is reported to illustrate the importance of such infections due to *B. megaterium* in the differential diagnosis of anthrax and to demonstrate that organisms which are generally considered non-pathogenic may, on occasion, assume enhanced virulence and become potentially pathogenic to humans.

The author is grateful to Dr. H. O. Dillenberg of the Province of Saskatchewan, Department of Health, Division of Laboratories, Regina, for his assistance in the investigation of this case and for providing information regarding the bacteriological characteristics and pathogenicity of the infecting organism.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

TEACHING BY PANTOMIME

Pantomime, that is, a series of actions, such as gestures and postures, for the purpose of conveying ideas or information, is the lowest form of expression. It is very commonly employed in conversing with persons who are deaf, with primitive peoples, and in the teaching of medicine.

Surgeons, in speaking of appendicitis, for example, are not content with mentioning McBurney's point, but place the hand upon their own anatomy between the anterior superior spine of the ilium and the umbilicus.—Excerpt from an editorial, *Canadian Medical Association Journal*, 1: 260, March 1911.

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LOWER NEPHRON NEPHROSIS DUE TO CONCENTRATED LYSOL VAGINAL DOUCHES: A REPORT OF TWO CASES

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OWING TO education of the public, to prenatal clinics and to constant research, maternal mortality has shown an impressive decrease over the past two decades, but mortality was still not inconsiderable in 1959. These maternal deaths are caused by a variety of complications of pregnancy and labour, one of which is abortion, particularly self-induced abortion which is frequently prompted by desperate social situations. This continues to take its annual toll of maternal life.

This report will present the case histories of two patients who tried to induce abortion by self-administered concentrated Lysol vaginal douches. Both cases were complicated by lower nephron nephrosis, and little is to be found in the literature in this connection.

Lysol is a commercial preparation consisting of a 50% mixture of cresol (a member of the phenol group) with linseed oil soap. As an antiseptic it is about three times as efficient as phenol. Its action is similar to that of phenol.

The toxicity of cresol is well known, and its action has been well described.[1] Besides the local corrosive action, kidney damage is frequently encountered, particularly if the chemical is ingested orally. Von Oettingen[1] mentions similar renal damage after intrauterine application of cresol but provides no case references or reports. According to him, a 2 to 3% phenol solution is sufficient to cause tubular necrosis. Presley and Brown,[2] in a partial review of the literature, reported only one case of the use of Lysol or other phenol compounds as abortifacients, in addition to three cases of their own. Vance[3] described one such case which was complicated by oil embolism. Witthaus and Becker[4] briefly mention three cases with one death. Other reports deal with soft soap pastes instilled in the uterine cavity to induce abortions. These pastes contained phenol compounds in negligibly small amounts (0.05%).[5] Such pastes were frequently used in Europe for therapeutic abortions in the 1920's. Though the foregoing may not constitute a complete review of the literature, in none of the cases reported were renal complications encountered.

CASE 1.—The first patient was a 32-year-old, single, para I, gravida II, French Canadian woman, in her sixth month of pregnancy. She was admitted through the emergency department of the Ottawa Civic Hospital with all the signs of an inevitable abortion. She confessed to having used a vaginal douche of a concentrated solution of Lysol in water. The first uterine contractions were noticed 12 hours later, and vaginal bleeding commenced shortly thereafter. The placenta and fetus were passed after 10 hours of labour. The day after admission renal shut-down became evident, urinary output being only 200 c.c. Three days later the blood urea nitrogen value and serum electrolyte patterns were consistent with a lower nephron nephrosis. The blood urea nitrogen reached a peak of 170 mg. %. On the sixth day in the hospital renal function began to improve and thereafter she excreted increasing amounts of urine each day. Within four weeks the serum electrolytes and renal function tests returned to within normal limits, and the patient was sent home. It should be mentioned that in this case there was shortly after admission the additional complication of afibrinogenemia, which was successfully treated by the administration of fibrinogen. She returned to the hospital three months later with serum hepatitis, but has otherwise remained well.

CASE 2.—The second patient was a 26-year-old French Canadian woman, married, but separated from her husband. She was para IV, gravida V, and 3½ months pregnant. She had used a vaginal douche of concentrated Lysol solution 25 hours before admission. On admission she complained of severe burning sensation in the area of vulva, perineum and adjacent thighs. On examination there was erythema of the thighs and vulva. Vaginal bleeding was moderate. Pieces of placental tissue were passed but the abortion remained incomplete. The day after admission renal shut-down became apparent, with a 24-hour urine volume of only 150 c.c. On the same day her blood urea nitrogen rose to 79 mg. % and reached a peak of 127 mg. % on the third day. A full-blown picture of lower nephron nephrosis developed rapidly in this case. Attempts to correct the electrolyte imbalance were in vain. The patient's condition deteriorated rapidly and she died on the sixth day in acute pulmonary edema. Postmortem examination confirmed the diagnosis of pulmonary edema and tubular necrosis. There was no evidence of peritonitis.

These two cases are reported to emphasize the importance of maintaining careful observations on renal function in all patients with abortions, even in the absence of shock. Thus renal shut-down may be detected early and treated properly. Otherwise such patients may easily be overhydrated, particularly in view of the current use of liberal intravenous infusions.

SUMMARY

Two cases of lower nephron nephrosis after a Lysol vaginal douche are described. One patient was sent home cured after four weeks in the hospital; the second died on the sixth day in the hospital. These two case reports draw attention to a complication of criminal abortion which may be more frequent than is generally realized.

I wish to express my thanks to Dr. York for permission to publish these cases.

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SHORT COMMUNICATION

CHLORAMPHENICOL THERAPY: A WARNING*

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IN THE literature since 1950 frequent articles indicating the danger of the indiscriminate use of chloramphenicol have been published.[1-3] As recently as April 1960 the Subcommittee on Blood Dyscrasias of the American Medical Association noted "the increase in the receipt of reports by the Registry on Blood Dyscrasias in which chloramphenicol is associated with the development of a blood dyscrasia".[4] This communication is a plea for the rational use of chloramphenicol.

At the Hospital for Sick Children, Toronto, in a 12-month period ending in June 1960, four children with blood dyscrasias probably due to chloramphenicol therapy were observed. Two children had agranulocytosis; the other two had aplastic anemia.

Recently there appears to have been an unwarranted increase in the use of chloramphenicol. The pressure from sales organizations of pharmaceutical companies has intensified. The prescribing of chloramphenicol imported from Europe appears to have greatly increased. One large centrally located Toronto pharmacy reports that the amount of chloramphenicol that was dispensed during October 1960 was two and one-quarter times the amount dispensed during October 1959. A further comparison between these two months did not reveal any appreciable difference in their total volume of business or in the amount of illness.

The chemical nature of chloramphenicol indicates that the drug can produce bone marrow depression. Krakoff *et al.*[5] have demonstrated that large doses of chloramphenicol have a depressant action on hematopoiesis. Four patients with inoperable and far-advanced cancer were given massive doses of chloramphenicol by mouth. The maximum daily dose varied from 6 to 12 g. The total dose per course varied from 47 to 184 g. The duration of the course varied from 10 to 35 days. Three of the four patients had two courses. All the patients showed a significant reticulocytopenia. Only one patient showed a decrease in the number of platelets and white blood cells. The drug had to be discontinued in the other three patients because of the appearance of glossitis. The glossitis and all the hematological changes were reversible with discontinuation of the drug.

Some authorities believe that it is usually the total amount of the drug given rather than an idiosyncrasy that is involved in producing a blood dyscrasia. Hodgkinson[6] recommended that in adults a total dose of 26 g. should not be exceeded; that in children the total dose should not exceed the equivalent of 100 mg. per kg. of body weight daily for seven days; and that the length of treatment should not exceed 10 days. Of the cases that he reported with blood dyscrasias, three of 19 adults and five of 10 children received less than this total amount of chloramphenicol. Only two of the aforementioned five children received chloramphenicol for more than 10 days. Since idiosyncrasy often seems more important than total dosage, Hodgkinson's recommendations have limited value.

Several investigators have been concerned with the problem of the hematopoietic response to chloramphenicol toxicity. Rubin *et al.*[7] have reported on the changes in iron metabolism in early chloramphenicol toxicity. Rosenbach *et al.*[8] have reported on two cases in which some unusual bone marrow changes were shown after chloramphenicol administration. They noted: "In both cases the bone marrow revealed indications of maturation arrest, with striking vacuolization of the erythroid elements; when the drug was discontinued, these changes disappeared, and the patients recovered. These findings may represent another recognizable early change of chloramphenicol toxicity."

The following is a summary of the hematological changes occurring as a result of chloramphenicol toxicity. These changes can be divided into three categories:

1. *Ferrokinetics*

A. Delayed disappearance of Fe^{59} from the plasma and delayed incorporation of Fe^{59} in the circulating red cells.

B. Elevation of the plasma iron with an increased saturation of the plasma iron-binding globulin.

2. *Bone Marrow*

A. Arrest in maturation of the erythroid series.

B. Vacuolization of the erythroid series (as well as of granulocytes and plasma cells)—estimated to be present in 50% of cases.

C. Hypoplasia with eventual aplasia.

3. *Peripheral Blood*

A. Fall in reticulocyte count resulting in anemia.

B. Leukopenia and/or agranulocytosis.

C. Thrombocytopenia.

The incidence of blood dyscrasias due to chloramphenicol therapy is low but not negligible. The incidence is reported to be between 1 in 100,000 and 1 in 10,000,[9] but these figures are probably meaningless because no adequate survey has been conducted.[1] Although the amount of the drug given, the length of time the drug is given, and whether the treatment is intermittent or uninter-

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rupted, are all probably factors in the incidence of hematopoietic reactions, the most important factor appears to be idiosyncrasy to the drug.

In an American survey which covered all severe reactions to antibiotics from late 1953 to early 1957, 72 deaths occurred from anaphylactoid shock caused by the intramuscular injection of a penicillin preparation and 25 deaths occurred from blood dyscrasias associated with chloramphenicol therapy.[10]

Scott *et al.*[11] conclude that in 5 of their 39 cases of acquired aplastic anemia, chloramphenicol was considered to be the probable causative agent. Rosenbach *et al.*[8] report that of 30 cases of aplastic anemia seen in their clinic between 1957 and May 1960, eight (27%) had been associated with chloramphenicol administration.

What is to be done to prevent the occurrence of blood dyscrasias due to chloramphenicol therapy? The most obvious and probably the best answer is that chloramphenicol should be resorted to only when the indications for its use are unequivocal. Each case considered for therapy must be assessed individually. If prolonged treatment, as in osteomyelitis, or if massive treatment, as in influenzal meningitis, are contemplated, the dangers must be weighed against the potential benefits. Errors in prescribing chloramphenicol and in neglecting to discontinue administration of the drug when indicated have been implicated in some cases where blood dyscrasias have occurred.

Most individuals can tolerate large doses of chloramphenicol for prolonged periods without ill effect. The difficulty appears to be in detecting the person who has an idiosyncrasy to the drug. Although a latent period of from five to eight weeks frequently occurs between the discontinuation of chloramphenicol and the appearance of symptoms of aplastic anemia, routine white blood cell counts, reticulocyte counts, and hemoglobin determinations (and possibly bone marrow examinations) when the patient is receiving the drug should be performed, because bone marrow depression may be reversible if the drug is stopped in time.

Aside from the toxic effect on the bone marrow, consideration should also be given to the following factors when chloramphenicol is prescribed:

1. *Its use for newborn and premature infants.*—With high dosage of chloramphenicol in premature and newborn infants, symptoms appear in the following order: abdominal distension, with or without emesis; progressive pallid cyanosis; vasomotor collapse, frequently accompanied by irregular respiration; and sometimes death within a few hours of onset of these symptoms. Some clinicians describe this condition as the "grey syndrome".[12]

2. *Proper dosage.*—Chloramphenicol dosage is not infrequently erroneously believed to be the same as that for tetracycline. The chloramphenicol dosage is generally twice the amount of tetracycline. The usually recommended dosage[13] of chloramphenicol by mouth for children over two years of age, for infections other than meningitis, is 100 mg. per kg. of body weight daily up to a maximum of 3 g. daily. The dosage for tetracycline by mouth is 50 mg. per kg. daily up to a maximum of 2 g. daily.

3. *Erratic absorption of palmitate.*—Even when lack of gastrointestinal enzymes is not suspected, the absorption of the palmitate has been reported as erratic in some cases.[14]

4. *The development of staphylococcal enterocolitis.*—An overgrowth of resistant staphylococci in the bowel has been observed, though infrequently, with chloramphenicol therapy.

This communication can be summarized by quoting the last paragraph of the 1960 report of the Subcommittee on Blood Dyscrasias of the American Medical Association: "Although the subcommittee recognizes that chloramphenicol is a valuable antibiotic, it is also the opinion of the subcommittee that there is no longer a reasonable doubt that chloramphenicol may cause aplastic anemia. Periodic blood cell counts may be of some help; however, they cannot be relied on to detect signs of marrow toxicity sufficiently early so that chloramphenicol administration can be discontinued before an irreversible aplastic anemia develops. Therefore, judicious use of the drug must be the rule, and it should not be used prophylactically, in trivial infections, or in infections in which other, less dangerous antibiotics may be used effectively."[4]

I wish to thank Drs. T. E. Roy, E. Wake and M. Tedeschini for their help and criticism in the preparation of this communication.

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CURRENT CONCEPTS OF IMMUNOLOGY: I. THE THEORY OF CLONAL SELECTION

AMONG THE most exciting and potentially far-reaching advances in the modern world of medicine are those that are unfolding in the field of immunology. The significance of these developments was recognized in the joint award of the 1960 Nobel prize in medicine to two brilliant exponents of this branch of medical science. These modern immunologic concepts have fundamental bearing on such a broad range of medical and surgical problems that it is proposed to review some of their highlights in a series of editorials in this and subsequent issues of the Journal.

The practical application of immunologic theory to clinical medicine had its origin late in the 18th century with Jenner's discovery of the principle of immunity, so dramatically demonstrated by the protection that his vaccine provided against smallpox.

For nearly a century and a half thereafter classical immunology evolved from the study of cellular, and more particularly of humoral, factors concerned in the defence of the organism against invasion of foreign substances, bacterial or chemical, from without. The pursuit of these studies was rewarded by considerable success so that, today, effective immunization techniques have been developed against most infectious diseases that are not controlled by public health measures or that are not susceptible to antibiotics or chemotherapy.

Largely in the past decade the concept of immunology has been expanded far beyond the narrow confines of immunization against infection. Thus the modern immunologist has become more concerned with the understanding of what happens to an individual when he becomes immune. He has learned that immune mechanisms may be harmful as well as beneficial or protective; he has begun to explore possible ways and means by which these mechansisms can be circumvented in the interests of therapy or surgical repair; and he is engaged in intensive studies of the manner by which their spontaneous malfunctioning gives rise to serious disease.

Modern orthodox immunologic theory holds that the central feature of immunity is the production of antibody by a specialized group of tissue cells, the plasma cells. Antibody can be identified by its physical properties as a gamma globulin, and each antibody has a specific affinity for the particular antigen that stimulates its production. An antigen may be part of a virus, bacterium or foreign tissue cell or it may be a protein or polysaccharide fragment of these moieties. Antibody protects the organism against foreign substances by combining with them and rendering them inactive. Both antigen and antibody consist of molecules composed of a large number of atoms and both possess molecular weights in the range of 160,000, i.e. about 10,000 times the weight of an atom of oxygen. The actual sites at which antigen and antibody combine with each other, however, represent only small portions of these complex molecules, equivalent to the region occupied by three to five of the several hundred amino acid units in an average protein or a comparably small number of the monosaccharide units in a polysaccharide. These small units where union takes place between an antigen and an antibody are known as "*antigenic determinants*" on the antigen, and as "*specific patches*" on the antibody, and they fit into each other as a key fits in a lock or like pieces of a jigsaw puzzle.

At this point there is a divergence of opinion concerning the mechanism by which the precise interlocking pattern between antigen and antibody is acquired. Arising out of the concepts of Ehrlich, Landsteiner and Pauling came the theory that the specific patch on the antibody acquires its pattern by being synthesized in contact with the antigenic determinant. This theory presumes that the antigen is taken into the cell and is incorporated into the globulin molecule while the latter is being assembled from amino acid units by the cell's machinery of synthesis. The globulin being brought into contact with the antigen is moulded into the appropriate complementary pattern. This is the simplest form of what Lederberg has termed the "*instructive theory*" of antibody formation; based on the concept that the information from which each specific antibody is constructed is supplied by the antigenic determinant itself, the latter "instructing" the cells concerned in the details of antibody manufacture.

It has been pointed out, however, that this "instructive theory" fails to explain several significant immunologic phenomena, such as the persistence of immunity long after the antigenic stimulus has been applied, and the origin of a group of disorders that have been attributed to immunological reactions of the body to one or more of its own components, the so-called *autoimmune diseases*. Accordingly a fundamentally different view has

been advanced in the *"selection theory"* of antibody formation which holds that antibody molecules, like any other protein molecules, are fabricated according to genetic instructions contained in the nucleus of the manufacturing cell. At no time does information from without enter the cell or influence antibody manufacture. Instead, for each one of myriads of possible foreign antigens the body already possesses a cell or a group of cells genetically capable of synthesizing the appropriate antibody. Each of these cells or cell groups "knows" how to make specific antibody even if the antigen never enters the body. The function of antigen, in this concept, is merely to *select* and stimulate proliferation of the appropriate group of cells, thereby leading to increasing production of the required antibody. These groups or "populations" of cells, which reproduce by asexual division, are referred to as *"clones"* and being equipped to respond to an antigen, they are spoken of as being *"immunologically competent"*.

Most proteins are antigenic to an organism that has not been concerned with their production. While capable of producing antibody against any protein or other substance of appropriate molecular character that is not present within it, the body does not normally produce antibodies against its own tissues. This implies that each individual organism possesses some mechanism whereby it can recognize and distinguish that which is *"self"* from that which is *"non-self"*. This mechanism has been likened by Jerne to a dictionary that the body must consult to decide whether a given "word" (i.e. chemical configuration) is foreign or belongs to its own language. Current thought holds that this dictionary lists only foreign "words", or patterns, in large numbers which among them can offer a complementary specific antibody patch to correspond with every possible antigenic determinant. The lymphocytes are the most likely carriers of the "words" or antibody patterns. In the early stages of embryonic development it is assumed that the ancestors of these cells are highly mutable, their genetic material changing spontaneously and in random fashion, creating all possible antibody patterns. Each mutated cell gives rise to a small group or *clone* of cells, all identical, and all carrying the pattern for one or, at most, a few specific antibodies. Because the mutation process is a random one it would create cells capable of making antibodies against antigenic components of the body's own tissues but such cells are destroyed by contact with their own antigen in the process of normal embryonic development. In other words, during an early embryonic phase, *"forbidden clones"* that match "self"-antigens are eliminated as they arise and this process is referred to as *"immunologic homeostasis"*. Foreign antigens may rarely reach an embryo, as in the case of non-identical twins sharing a single placenta, in which case they come to be accepted as "self". Later in embryonic life the rate of mutations in these "immunologically competent" cells decreases to that of all other adult cells of the body. (It has been estimated that up to a million cells in the normal adult body undergo mutation daily.) "Forbidden clones" would thus continue to arise, but with less frequency, and would normally be destroyed or inhibited while still immature. Once immunologically competent cells reach maturity, however, rather than being destroyed by their appropriate antigen, they are stimulated by it to proliferate, producing among their offspring large numbers of the plasma cells that probably manufacture the actual antibody molecules which combine with and de-activate foreign antigens.

This hypothesis is called the *Clonal Selection Theory* because the action of the antigen is solely to select for proliferation that particular clone of cells which can react with it.

Occasionally this mechanism of immunologic homeostasis whereby the body recognizes "self" components becomes deranged, with the resulting production of a group of disorders termed "autoimmune diseases". The clonal selection theory postulates that this phenomenon occurs when a "forbidden clone", through mutation or some other mechanism, achieves a state of abnormal protection from destruction or inhibition by its corresponding antigen.

In the words of Sir Macfarlane Burnet, whose studies have developed the clonal selection theory of immunity to its present state: "This may be a mere cobweb of phantasy, but in my more optimistic moments I can hope that it may also function like Ariadne's thread to guide us effectively through part of that biological labyrinth, the process of differentiation."

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SOME ASPECTS OF MEDICAL SERVICES IN PRESENT-DAY RUSSIA

IN January 1960 a series of resolutions was adopted by the Council of Ministers of the Union of Soviet Socialist Republics, with the objective of improving health protection and medical services for Soviet citizens. Discussing these resolutions, N. A. Vinodradov, Minister of Health of the Federation of Russian Socialist Republics (to be distinguished from the Union of Soviet Socialist Republics), concentrated on the shortcomings of medical clinics (known as "ambulances" in the U.S.S.R.) and hospital outpatient departments (or "polyclinics") (*Sovetskaya Meditsina*, 8: 3, 1960).

The vast majority of Russian citizens are under the medical care of physicians whose distribution throughout the Russian Federation, he said, is far

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from satisfactory. Although in smaller cities there is one doctor for each 4300 citizens, in some of the more remote autonomous republics and districts there may be as many as 5000 to 8000 persons for every physician. Redistribution of medical personnel is being undertaken but to date has not been accomplished satisfactorily. Diagnostic, prophylactic and therapeutic services have been greatly improved in many outpatient centres but still leave much to be desired in the majority of these institutions. A major problem to be solved is the overburdening of district physicians and the medical staffs of clinics and hospital outpatient departments with such duties as the completion of forms and certificates, which reduces the time they can devote to clinical activities. It was recommended that district physicians should be spared the time-consuming duties of building inspections and similar prophylactic health measures which should be taken over by sanitary workers. Pre-employment medical examination of every industrial worker was not considered necessary by the Health Minister, who felt that such examinations are required only by applicants for potentially dangerous occupations.

In the past 10 years the numbers of medical personnel in outpatient services has increased by 46.9%; over the same period there has been a 71.1% increase in hospital medical staff although hospital bed accommodation rose by only 54%. These data were taken to indicate the need for more effective utilization of physician services in the various medical institutions.

The necessity of raising standards of qualifications of district physicians and doctors working in hospital outpatient departments (polyclinics) was also emphasized. Most of the latter are now incorporated in central hospitals where they provide fundamentally important facilities for postgraduate teaching. Throughout the cities of the Russian Federation of Socialist Republics there is still a major shortage of housing accommodation for outpatient institutions. In some cases a single room is used simultaneously by two doctors, to the detriment of their psychotherapeutic efforts and their authority in dealing with individual patients.

Of basic importance in the outpatient organization is the district physician (the Soviet equivalent of the family doctor). The Health Minister of the Russian Federation considered that his Ministry had underestimated the role of the district physicians and had failed to create conditions necessary for the efficient conduct of their work, with the result that the number of such doctors has not been increased to the minimum required for the adequate care of the population dependent on their services. He announced his Ministry's intention to devote its attention and efforts towards improvement of qualifications and working conditions of the district physicians and described its plans to relieve these doctors of many of their present duties not immediately associated with therapeutic and preventive medicine.

He recommended further that young physicians should not be permitted to engage in practice immediately after graduation but should spend at least six months in postgraduate training in a hospital setting.

The Minister then announced the following plans for future development of medical services in the Russian Federation. In every city with a population over 200,000 there will be one "polyclinic" with an "organization centre" for special statistical research to evaluate the efficiency of the community's medical care. For every 50,000 citizens the services of a urologist and of an endocrinologist will be available for adults and children. Cities of 200,000 or more will be provided with traumatological services, and by 1962, stomalological (dental) services will be available, particularly for children, in all major centres. Dispensaries will be opened in outpatient departments, and sales of "hygienic and sanitary articles" will be increased. Hospital doctors will be allowed to issue certificates of incapacity for work, for periods up to 10 days, and chief physicians will have authority to extend this period to 15 days. A network of medical and industrial health points will be created for the protection of workers, particularly those employed in industrial enterprises.

Closer liaison between medical scientists and practitioners is being promoted in Rostov by the patriotic academic staff of that city's Medical Institute who, in addition to their regular teaching duties, act as consultants in the city's hospitals and outpatient departments, thereby extending the benefits of their skills to the provision of clinical care for patients and graduate teaching of the doctors in outlying districts. This type of program was acclaimed as an example for the rest of the nation.

Regardless of his specialty, proclaimed the Health Minister, every doctor must familiarize himself with the principles of prophylactic or preventive medicine as well as those of diagnosis and treatment. Medical institutes, he said, must become centres of health culture and education of the public in hygienic principles. He referred to some "300 universities of health" in which over 500,000 citizens each year study the basic features of hygiene and preventive medicine, as an example of co-operation between party and populace.

In concluding his remarks the Minister observed that "the government has issued a decree which it is our duty to carry out, indeed to exceed, for the benefit of the people of our country who are building the communist society."

This lengthy and forthright address provides an intriguing glimpse of some of the facets of the state-controlled program of medical services as it exists in Russia today, and of the forces that direct and guide it. W.G.

LETTERS TO THE EDITOR

INTRAVENOUS HUMAN FIBRINOLYSIN IN THE TREATMENT OF INTRAVASCULAR THROMBOSIS

To the Editor:

I would like to comment on the article by Drs. Watt and MacMillan (*Canad. M. A. J.*, 83: 1436, 1960) which reported "no objective evidence of improvement" in any of 10 patients with "recent intravascular thrombosis" when treated with fibrinolysin. This communication also reported febrile reactions in 7 of the 10 patients.

It goes without saying that the advent of an effective and harmless agent for dissolution of intravascular clots would be an advance of the first magnitude. I trust, therefore, that the results obtained by these authors will not be accepted without a second look at the evidence.

The high incidence of febrile reactions makes me suspect that the material used was from research batches prepared a few years ago, because these batches were found by several workers to give this type of trouble and because with the present commercial product such reactions are exceptional. Of seven patients personally observed, not one showed a febrile reaction.

It would be pertinent to ask how after the onset of thrombosis the fibrinolysin was administered, because it is taken that treatment must be started before epithelialization has occurred—as soon as possible, in other words, and certainly within four to five days.

It is now well documented that venous thrombosis is more susceptible than is arterial and that dosage for arterial lesions must be substantially greater. Of my own seven cases, there was no demonstrable benefit in two instances of surgery on diseased arteries, but this is hard to evaluate; there was apparent reduction in size of a visible clot in a retinal arteriole so that it moved from astride a bifurcation on into one of the branches; there was clear improvement in all of four cases of massive pulmonary embolism and, indeed, in one patient the effect was probably life-saving as far as could be judged by the attending physician.

An excellent and conservative evaluation of the present status of fibrinolysin therapy was afforded us in Montreal when Dr. K. M. Moser delivered the Hingston Memorial Lecture at St. Mary's Hospital last November. His experience parallels that reported in the symposium cited[1] and refutes the completely negative results of Watt and MacMillan. While I have not myself carried out *in vitro* testing, I understand that this is by no means easy to accomplish and that results have varied widely from one laboratory to another. Of the many recent papers on the subject of fibrinolysin, I append two references in particular[2, 3] which warrant attention.

CECIL HARRIS, M.D., F.R.C.P.

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To the Editor:

Dr. Cecil Harris is correct in his suspicion that the fibrinolysin "Actase" used in our study was research material. We did not test the commercial product clinically but found, *in vitro*, that it was unable to dissolve fibrin.

The method used for *in vitro* tests was the standard, widely accepted fibrin plate method evaluated by Astrup (*Physiol. scandinav.*, 21: 238, 1950). Results with this method do not vary widely from one laboratory to another. We repeat that material described as fibrinolysin (Plasmin) should be capable of dissolving fibrin *in vitro*. So far, in repeated testing of different lots neither research nor commercial Actase has shown this property. Slight streptokinase activity has been noted and the beneficial clinical effects described by some investigators could be due to streptokinase. If this is so, then Actase is an expensive way to provide streptokinase.

In all cases the drug was started within 24 hours of the clinical manifestations of the thrombotic process.

We question Dr. Harris' interpretation of "clear improvement in four cases of massive pulmonary embolism". Most of the patients who survive the acute attack recover completely on anticoagulant therapy alone.

Refute means to prove in error. Our completely negative results are *not refuted* by Dr. K. M. Moser's experience. Each reported series stands on its own merits. We agree with Dr. Harris' advice to take a second look at the evidence. This is what the reader will do to arrive at his own interpretation of the results.

R. L. MACMILLAN, M.D. and
DAVID L. WATT, M.D.

284 St. Clair Avenue West,
Toronto.

STRABISMUS AS A COMPLICATION OF INFLUENZA

To the Editor:

Last November and December, influenza was prevalent in the Chinook Health Unit area (Town of Fort Macleod and district in Southern Alberta). It affected mainly and most severely children between the ages of one and six years.

The signs and symptoms were fairly constant, consisting of a sudden onset with anorexia and pyrexia (between 103 and 105.5° F.) and often accompanied by gastrointestinal disturbances such as vomiting and diarrhea. The acute phase usually lasted from three to five days. It was noted that several children developed a definite and marked squint. This complication had also been noted by some of the local physicians. On checking these children it was found that the squint disappeared completely in four to six weeks.

Central nervous system complications, especially encephalitis, are well known but I have never seen strabismus reported following influenza. When this complication is encountered for the first time it may give rise to concern, and it might be useful to know that the strabismus is only of a transient nature.

Chinook Health Unit,
Blairmore, Alta.

K. ADLER, M.B., D.P.H.,
Medical Officer of Health.

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Canadian Government Travel Bureau, Ottawa

Visitors view Montreal from the lookout atop Mount Royal.

COME TO MONTREAL!

FOR THE 94th ANNUAL MEETING OF THE CANADIAN MEDICAL ASSOCIATION

JUNE 19-23, 1961

THE SCIENTIFIC PROGRAM

For some months the Central and Local Program Committees of the C.M.A. have been concentrating on a Scientific Program designed to acquaint general practitioners with new developments in diagnosis and treatment. These Teaching Sessions will commence on Tuesday morning, June 20, and will continue throughout most of the following three days. As they are in the nature of refresher courses they will embrace panel discussions on medicine, surgery, pediatrics, anesthesia, obstetrics and gynecology.

The General Sessions on Wednesday and Thursday will include three special speakers in medicine, anesthesia and psychiatry. On Thursday morning, the Lister Oration will be presented by Dr. Hugo Rosenqvist, distinguished surgeon-in-chief of the South Hospital, Stockholm, Sweden. Other General Session speakers will include: Dr. Charles M. Fisher, Department of Neurology, Massachusetts General Hospital; Dr. LeRoy D. Vandam, Department of Anesthesiology, Peter Bent Brigham Hospital, Boston; and Dr. D. Ewen Cameron, Allan Memorial Institute, Montreal. Friday, June 23, has been set aside as Medical Economics day, which will include a number of addresses and panel discussions on medical services insurance and other economic matters of topical interest. At this time, the Hon. Emmett M. Hall, Chief Justice of the Province of Saskatchewan, will speak on "The Role of the Royal Commission on Health Services". Chief Justice Hall was recently named Chairman of the Royal Commission on Health Services, by Prime Minister Diefenbaker. On the same program, Dr. T. J. Quintin, a member of the C.M.A. Executive, will talk on "Health Insurance in Australia"; and Dr. Hugo Rosenqvist will speak on the same subject insofar as Sweden is concerned. Other medical economics topics will include "Government and Medicine" and "Existing Deficiencies in Health Services – the Saskatchewan Experience". Another Scientific Program feature will be the showing of several medical films dealing with clinical topics.

THE SOCIAL PROGRAM

The Planning Committees in Montreal have also arranged a number of interesting social events, which will commence on Monday evening, June 19, when members and their wives will participate in a wine-tasting supper party. This event will take place in the Museum of Fine Arts, and those present will have the opportunity of tasting some twelve different imported wines accompanied by a similar number of cheeses. The meal will be rounded out with special hors d'oeuvres and pastries. On Tuesday evening, the Annual Dinner to the General Council will take place in the Ballroom of the Queen Elizabeth Hotel, and special musical entertainment has been arranged for this occasion. All are invited. The highlight of our convention week will be the Annual General Meeting, which will commence at 8.15 p.m. on Wednesday, June 21. At this time the colourful ceremony of the installation of the President will take place; and His Excellency Major-General Georges P. Vanier, D.S.O., M.C., C.D., Governor General of Canada, will be made an honorary member of the C.M.A. It is interesting to note that this is only the third time in the history of the C.M.A. that a non-medical person has been awarded this honour. The other two honorary memberships were presented to the Right Honourable Vincent Massey, former Governor General of Canada; and His Royal Highness The Prince Philip, Duke of Edinburgh. In addition to the above, the Canadian Medical Association will honour its Senior Members who have been nominated by their respective Divisions.

Details of the ladies' program will appear in a later edition of the Journal along with other program highlights.

BIENVENUE À MONTRÉAL

C.M.A. delegates visiting Montreal for the first time will find it historical and gay. On every side you will encounter the bilingual character of Montreal–in

(Continued on page 561)

VIEWS ON THE ECONOMICS OF MEDICINE

Prepared by the Department of Medical Economics. The Canadian Medical Association

MAR. 11, 1961, NUMBER 16

Our sources of information are private communications and published comments in medical journals and the lay press. These are usually reliable but incorrect quotation or interpretation is always possible.

The following is the resolution of the Policy Committee for submission to the National Liberal Rally in Plenary Session and approved January 10, 1961:

Second only to the threat of unemployment is the threat of illness. Hospital insurance, which has now become available to all Canadians, does much to lessen the insecurity of ill health. But it is not enough. Many people still face medical costs, outside the hospital scheme, that are financially crippling to them. While various good schemes of prepaid medical care are in operation, they are not available to everyone, on terms everyone can afford. In consequence, there are still many Canadians who go without medical care that they need; and others, whom serious illness forces to go to a doctor, are thereby pushed into overwhelming debt or a catastrophic impairment of their savings.

It is Liberal policy to end such social evils. Universal hospital insurance was a big step forward. Further measures are needed to reduce the insecurity arising from illness. A new Liberal government will undertake at once, to provide extended hospital facilities, including mental health and rehabilitation, comprehensive care by doctors, drugs and medicines and diagnostic services.

Canadian doctors are rightly anxious that no new scheme will disturb the proper relationship of doctor to patient, or reduce the quality of medical care. The Liberal plan, therfore, provides that doctors will continue to be remunerated on a fee-for-service basis. The only difference is that the established independent commission or board of government, instead of the patient, will pay the doctors' bills, according to an agreed scale of fees, such as voluntary prepaid medical schemes provide at present.

Drugs and medicines are about as big an item as doctors' bills in the health care of the Canadian people. They deserve equal priority in a comprehensive health plan. It would, however, require too much red tape to try to keep track of all small drug purchases. A new Liberal government will therefore provide that all medicines and drugs prescribed by a doctor, beyond a low minimum value, will be paid for under the proposed health plan.

The greater part of the cost of a health plan will not be a new burden on the economy, for it will simply replace doctors' bills and medicine costs which are already being paid by individuals, either directly or through pre-payment schemes. However, there will be some increase, because some people will be getting treatment they need but cannot now afford. This, of course, is the purpose of the scheme. There may be also some tendency for a small minority of people to abuse the scheme by seeking care they do not really need. The method of financing the scheme will be designed to reduce any

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such tendency as much as possible, and at the same time be equitable to all.

One possible method of finance would be similar in principle to the present treatment of family allowances and old-age pensions. These are paid to everyone, but people with relatively large incomes pay higher taxes than they would pay if they did not get the allowances or pensions.

On this principle, everyone could be required, when making out an income tax return, to report on his income tax form the total of the doctors' and druggists' bills that the government has paid on his behalf during the year. He would then pay tax on this amount, at the same rate as he pays on the top step of his actual money income. In this way, nothing will be required from people whose incomes are below the taxable level, while wealthy people, with incomes in the high tax brackets, will in effect still pay more of their medical costs themselves. Such people can, of course, continue their private insurance coverage for the balance of their medical expense.

By such a device as this, the cost of the scheme can be kept down, and abuses held to a minimum, without red tape and in a way which ensures that it's those most in need who are helped most.

A new Liberal government will meet the rest of the cost of this health plan out of general tax revenues. It will not impose a special premium or ask the provincial governments to contribute.

But the application of the scheme will, of course, be worked out with the provincial governments under the provisions of B.N.A. Act. It will be designed to ensure that the medical profession through its duly elected representatives, plays its rightful part in administration.

This national plan must in no way interfere with the doctors' freedom to provide competent care for their patients.

Professional standards and responsibility must not be infringed in any way. The doctor will be as free as ever to choose the place and type of his practice and his patients, and every patient will be free to choose his doctor, changing as he wishes. The patient will be free to go to specialists, whether inside or outside the scheme. Anyone who prefers not to take advantage of the scheme, but rather to go on paying his doctors' bills directly, will be free to do so. The scheme will, in short, make just one fundamental change: with the government assuming the responsibilites of payment, medical effort will be fully and naturally aimed at continuing to provide the highest possible standard of medical service to all Canadians, regardless of financial status.

Federal health insurance should be established in consultation with present prepaid health plans.

A new Liberal government will implement this health plan after taking office. The plan should not be delayed, or stalled until after a report from another Royal Commission. A new Liberal government will be ready to put this health plan into effect quickly, but with the administrative care that a sound system of this sort requires.

Other lines of attack on ill-health must be pressed forward at the same time. There is much to be done in the fields of mental health, preventative medicine, and rehabilitation after serious illnesses.

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Legislation regarding drugs will be strengthened to ensure high standards, to enable the public to know what it is buying and to avoid unnecessary costs.

A scheme covering doctors' services and drugs is not, of course, complete health care. A new Liberal government will co-operate with the provinces and the profession in encouraging dentistry, and as soon as possible will add dental services, with priority for children, optical services, and adequate nursing services, to the scheme.

There is still another major need in this field. The cost of ill-health does not lie only in the medical expenses and other charges that the sick person incurs. Just as serious, in many cases, is the loss of income while ill. A political party that is genuinely Liberal, and therefore practical too, does not pretend to the electorate that everthing can be put right at once. A new Liberal government will first of all get the health plan working properly, to ensure that no financial barrier will prevent any Canadian from obtaining proper treatment. But its next objective, hardly less important, will be to institute a comprehensive and adequate scheme of income maintenance during illness.

WELFARE STATE PROMISES

Quoted from Canadian Actuarial Bulletin, William M. Mercer Ltd., Volume 11, No. 2, February 1961.

Welfare state promises played an important part at the National Liberal Rally at Ottawa early last month. The principal plank in the Liberal platform for the next Federal election will be a national medical insurance plan.

The Liberals promised a medical plan covering doctors' bills and prescribed drugs. They did not announce the estimated cost but did say it would be met out of general revenue with no direct premium. Rough estimates of the cost can be made.

We can assume that our citizens would use a government-underwritten medical plan to at least the same extent as those that are covered presently use the doctor-sponsored prepaid medical plans. We can assume that the doctors' incomes would not be reduced, that the public and the doctors would not be any more willing (perhaps less willing) to control excessive utilization than they are now under their prepaid plans and that the expanded need for more doctors would be met by immigration and a speed-up in medical school graduations. The present doctor-sponsored prepaid plans cost in the area of $10 per month per family. If we assume Canada's population of 18 million is medically equivalent to 4½ million families, we come up with an annual cost for doctors' bills of something like $1/2 billion. It's a bit more difficult to estimate the cost of prescribed drugs but one plan in Canada (which, by the way, imposes a deterrent charge of 35c per prescription) finds it necessary to charge about $5 per month per family to cover this service. Using this plan as a guide, the free availability of prescribed drugs could cost about $1/4 billion per year.

It looks, then, as though the Liberals are talking about an initial medical plan (dental, optical and nursing services are promised for later) costing in the area of $3/4 billion per year. Personal income tax presently yields in the area of $1½ billion per year so that, on the face of it, it looks like revenue equivalent to an

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across-the-board increase of 50% in personal income tax would have to be collected and/or diverted to finance such a medical plan. The Liberals spoke, of course, of a device which would place the greater part of the cost on higher-income taxpayers. But this can only be carried so far. If the whole $3/4 billion had to be raised as new money (that is, if it could not be offset by decreased expenditures elsewhere) and if it were to be raised by doubling income tax on higher income citizens (impossible, of course, for those few citizens already paying over 50% tax), all Canadians with annual incomes down to about $5,000 would find themselves in the "higher-income" group, and their income tax doubled- or some other equivalent increase in their taxes.

The Liberals passed over the problem of who would control the doctors. As anyone in this field knows, insured medical care requires control-often unpleasant and unpopular-over the doctors as well as the users, and control by government would probably be even less popular than the control which the prepaid doctor-sponsored plans attempt to exercise at present. Then there is the constitutional problem that in Canada medicine is a matter of provincial jurisdiction.

Apart from medical care, the Liberals also approved the institution, within two years of taking office, of a contributory pension plan to provide all citizens with pensions at age 65. The contributions would be made by employees, employers, the self-employed "and by the government". The resolution talked loosely about integrating existing private pension plans with the new national scheme. Depending upon what this might mean, some employers (and in the case of union-negotiated pension plans, some unions) may decide to be particularly careful to guard against undue over-funding of their pension plans while there is still time.

The Liberals also promised lower taxes.

DOUGLAS CLAIMS HEALTH PLAN WEIRD TRAVESTY

Quoted from Toronto Globe and Mail, January 12, 1961.

"Premier T.C. Douglas of Saskatchewan today described the Liberal Party's proposed health insurance scheme as a weird travesty on a medical plan.

"Premier Douglas said he does not know how the plan would be put into effect and doubts that the Liberals do. He said it is not a health insurance plan at all, but a means of picking up bad debts for doctors.

"He said that the Liberal proposal makes no provision for improving the standard of care, integrating preventive and curative services, and giving the people a feeling of ready access to medical care."

SOAK THE SICK

Quoted from Toronto Telegram, January 14, 1961:

"'A soak-the-sick service' is how a top New Party man describes the new Liberal medical care plan unveiled at their rally in Ottawa."

"Morden Lazarus, political action director of the Ontario Federation of Labour, says:

'The more sickness, the more serious the ailment, the more money families tending to be poorly will have to pay under the plan.'"

(Continued from page 556)

speech, in press, in street names and signs, in cuisine and entertainment.

Montreal was originally the site of the Indian village of Hochelaga, and was founded as the city of Ville Marie de Montréal, on May 18, 1642, by Paul de Chomedy, Sieur de Maisonneuve. It was incorporated as the City of Montreal in 1832, and was the seat of the Government of Canada for several years after the union of Upper and Lower Canada in 1841. Today Montreal has a population of more than 1,700,000 of which two-thirds are of French origin.

Montreal has many points of interest for the out-of-town visitor. One of the city's chief attractions is St. Joseph's Oratory, a shrine dedicated to Brother André, which is visited by some three million people each year. Other points of interest include: Château de Ramezay, Montreal's well-known museum; Lookout Point at the top of Mount Royal; the Botanical Gardens; Dominion Square; waterfront and harbour; and the Montreal Museum of Fine Arts, which has regular presentations of various types of art and culture.

On the lighter side, Montreal is reputed to have more night clubs per capita than any other city in North America; and it is famous for its cuisine. Many of the cafés, night clubs and restaurants are located in a very compact area in the heart of the city.

More about Montreal in subsequent issues.

MEDICAL MEETINGS

THE CANADIAN SOCIETY FOR CLINICAL INVESTIGATION

The continued growth and activity of the Canadian Society for Clinical Investigation since its earlier days as a small informal travel club in the not too distant past, reflects an encouraging development of medical research in Canada. The dilemma of the committee responsible for the program of the 1961 annual meeting is further evidence of the healthy state of clinical investigation in this country, for in its selection of the 23 papers included on this year's program the committee was forced to relegate an even greater number to the "read by title" category. The 1961 meeting was held in the Château Laurier in Ottawa on Wednesday, January 18, 1961. The following officers were elected to the Society's executive for 1961-1962: Past-President, Dr. R. J. Slater, Toronto; President, Dr. Jacques Genest, Montreal; Vice-President, Dr. R. W. Gunton, Toronto; Secretary-Treasurer, Dr. Reuben Cherniak, Winnipeg.

Scientific Program

Drs. C. R. Scriver and I. A. Schafer of Montreal reported on studies indicating the likelihood of a common renal tubule amino acid transport system for proline, hydroxyproline and glycine. Normal subjects were rapidly infused intravenously with L-proline and renal clearances were calculated for plasma amino-acids before and immediately after infusion. Renal clearances of glycine and hydroxyproline were immediately but temporarily increased, simultaneously with greatly increased proline excretion. Clearances of other amino acids were not significantly altered. Complementary but less dramatic results were obtained with equimolar glycine infusions. Supportive evidence for the existence of this transport system was found in three unrelated clinical disorders, Hartnup disease, adolescent osteomalacia and familial hyperprolinemia.

Dr. W. A. Cochrane of Halifax described the results of a study on patients with cystic fibrosis carried out in an attempt to determine any significant changes in body composition that could be considered specific for this disease entity. Thirteen malnourished infants and children with cystic fibrosis presented the following specific findings: (a) increased plasma volume, (b) slight increase in body water, (c) moderate increase in extracellular fluid, (d) marked increase in total exchangeable sodium and (e) marked reduction in total body potassium. Four moderately well nourished cystic fibrosis patients had values similar to those of normals. It was considered that these abnormal changes in body composition are related to undernutrition and are not specific for cystic fibrosis. Evidence was presented suggesting that inability of the kidney to concentrate hydrogen ion is an effect of chronic cellular potassium depletion.

A series of experiments performed to study the effect of parathyroid hormone on phosphate excretion in thyroparathyroidectomized dogs was reported by *Drs. A. G. Ramsay, A. H. E. Samiy, P. F. Hirsch and J. P. Merrill.* These studies indicated that parathyroid hormone inhibits proximal tubular reabsorption of phosphate but has little significant effect on the transport of phosphate in the distal tubule.

Drs. W. M. Paul and A. Rapaport of Toronto described an investigation of the constituents of amniotic fluid to determine whether such changes might indicate any decreases in uterine blood supply. In experiments involving both partial and total ischemia of the uterus the most significant changes in the amniotic fluid were rises in the lactate/pyruvate ratio and in "excess lactate". Absolute lactate levels alone were not significantly elevated under the conditions of these experiments.

Studies of the liver and blood of animals poisoned by injection of carbon tetrachloride into the duodenum were reported by *Drs. A. Maximchuk and D. Rubinstein* of Montreal. The earliest change was a rapid loss of liver glycogen which was significant by two hours, accompanied by a small but significant elevation in blood glucose but no evidence of lactic acid accumulation in the liver or blood. Neutral fats and serum glutamic pyruvic transaminase also increased at this time. Serum isocitric dehydrogenase was greatly in-

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creased in eight hours. Respiration of liver slices decreased to a minimum in 16 hours, then began to rise again.

In a study described by *Drs. D. M. Tod and C. M. Couves* of Edmonton, Walker 256 carcinosarcoma was transplanted into the hind limb of male Sprague-Dawley rats which were then subjected to isolation and perfusion of the tumour-bearing area. The effects of variables, including length and time of perfusion, oxygen content and temperature of the perfusate, leak into the systemic circulation and specificity of the perfused drug, were observed in 400 perfusions. Rats treated with chemotherapy (TSPA) showed a marked decrease in incidence and extent of pulmonary metastases with increased survival times. Nodal metastases were increased in extent when amputation was performed, despite adjunctive chemotherapy.

Drs. T. Sandor and A. Lanthier of Montreal presented a report describing the formation of water-soluble conjugates of aldosterone and tetrahydroaldosterone, *in vitro* and *in vivo*. The *in vitro* studies were carried out by incubation of aldosterone with liver slices from dogs and humans and with human kidney slices. *In vivo*, d-aldosterone was administered intravenously to an adrenalectomized subject and urine was analyzed for unchanged and conjugated aldosterone.

Metabolic studies of two patients with primary aldosteronism due to adrenal adenoma were reported by *Dr. K. A. Evelyn* and his co-workers of Vancouver, before and after adrenalectomy. Preoperatively a moderate increase in potassium intake with or without reduction in sodium intake brought the serum potassium within normal range. Postoperatively one patient showed further serum potassium increase even though the potassium balance was negative. The ability to concentrate and acidify the urine improved gradually till a normal state was reached six months after operation. In one case PSP excretion and creatinine clearance fell sharply after operation and remained below preoperative levels for 13 months, although improving. The blood pressure returned to normal in one patient after operation but was unaffected in the other who had known mild hypertension of long duration before the symptoms of aldosteronism appeared. The response of sodium excretion after an intravenous salt load was influenced by the level of the blood pressure, rather than the degree of aldosterone excretion.

The effect of hypophysectomy in a severe juvenile diabetic on the metabolic response to monkey and human growth hormone was described by *Drs. McGarry and Beck* of Montreal. The results of this investigation suggest that monkey and human growth hormone differ in their effect on carbohydrate metabolism, that the presence of the pituitary modifies the changes in carbohydrate moieties by human growth hormone and that these changes are not those of spontaneous ketosis *per se* in the hypophysectomized patient but may be dependent on adrenal cortical secretions.

In a study of pituitary cytology, *Drs. C. Ezrin and W. C. Nicholas* of Toronto described three types of basophils and reported their investigations of the specific hormone production by each of these cell types. The evidence indicates that delta cells are associated with production of FSH and LH, that Beta 1 cells are concerned with ACTH production and that Beta 2 cells are linked with the manufacture of TSH.

The effect of insulin on glucose output by the liver and on the peripheral utilization of glucose was investigated by *Drs. G. Komaromi, N. Heller, T. Csorba and N. Kalant* of Montreal, by studies of the rates of entry and removal of glucose from plasma, using arterial blood samples taken before and after intravenous injection of glucagon-free insulin while the patient was receiving an intravenous infusion of C^{14} glucose. Most subjects responded to insulin with an increased rate of removal of glucose and decreased rate of entry of glucose into the plasma, suggesting that insulin has two separate effects in controlling the level of blood sugar.

In an electron microscopic study of muscle biopsies obtained from diabetic and non-diabetic subjects, *Drs. S. A. Bencosme, J. Kerr, R. O. West and D. L. Wilson* of Kingston, Ontario, observed in the diabetic patients a capillary lesion characterized by marked thickening of the basement membrane.

Dr. W. H. Francombe of Montreal reported the results of his investigation of the extravascular distribution of I^{131}-labelled albumin after its injection in dogs. The total extravascular space was found to contain 1.2 × the albumin in the plasma. Of the total albumin, 45% was found to be in the plasma, 25% in skeletal muscle, 15% in the skin and 8% in the gastrointestinal tract. None was found in the central nervous system, and very little in bone. In animals depleted of protein by plasmaphoresis the ratio of extravascular to intravascular albumin was reduced from 1.2 to 0.8, the loss occurring mainly from skin and gastrointestinal tract.

Observations on copper metabolism in two patients and 25 normal close relatives of patients with Wilson's disease were described by *Drs. A. Sass-Kortsak, B. S. Glatt and H. Ghadimi* of Toronto. In a high percentage of the heterozygous individuals there was a delay in the rate of incorporation of copper into ceruloplasmin following a single oral dose of Cu^{64}. After a single intravenous dose of Cu^{64} in a patient with Wilson's disease, only 70% of the dose was accumulated in the liver and less than 2% was in the plasma and erythrocyte compartment or was lost by excretion, between 10 and 60 hours after administration; 28% of the dose was not accounted for.

An interesting investigation of the allergenic component of raw coffee beans responsible for the frequent development of occupational asthma, rhinitis or dermatitis in workers in the coffee industry was reported by *Drs. S. O. Freedman, J. Krupey and A. H. Sehon* of Montreal. The allergenicity of raw coffee was attributed to tannins or related polyphenolic glycosides, at least in part. Chlorogenic acid was believed to be the main, if not the sole antigen of this chemcal group responsible for the clinical manifestations and it was suggested that this substance acts as a hapten. Presumably its antigenic activity is destroyed by roasting, since allergic workers showed no reaction to roasted beans on any of the tests employed.

A method for the estimation of *in vitro* survival of marrow cells, utilizing autoradiographic detection of tritiated thymidine uptake, was described by *Drs. L. F. Bélanger, R. K. Smiley and J. M. Martin-Villar* of Ottawa. The percentage of labelled cells was used as a criterion of the ability of the cells in a given marrow

aspirate to synthesize DNA and to divide. The effects of temperature, centrifugation, time of incubation, heparin concentration and the suspending medium, on the properties of marrow cells were studied. Most of the labelling of marrow cells took place after the first hour of incubation. At 4° C. no appreciable labelling occurred between 1 and 24 hours.

Drs. M. R. Becklake, C. J. Varvis, M. McGregor and D. V. Bates of Montreal reported on the development of a foreign gas technique for measurement of pulmonary blood flow utilizing a test gas mixture of nitrous oxide, oxygen and helium. The special features of this technique make it particularly suitable for studies during hard physical work, free of certain of the disadvantages of dye dilution techniques, including the inconvenience and discomfort of multiple venipunctures.

The cardiopulmonary physiological responses of anemic subjects to heavy treadmill exercise were described by *Drs. B. J. Sproule, J. H. Mitchell and W. F. Miller* of Edmonton. The results of this study suggest that either anemic persons perform work at less total energy cost and thus greater mechanical efficiency than do normals, or there is an alteration in intracellular intermediary metabolism so that there is a lag in the appearance of acid metabolites in the peripheral blood of exercising anemic individuals.

Drs. G. A. Sears, E. Carroll, J. C. Coles and G. W. Manning of London presented an impressive audiovisual demonstration of their intracardiac phonocardiographic studies of the aortic valve in normal dogs and in dogs subjected to removal of part of an aortic cusp, in addition to selected left-sided intracardiac phonocardiograms from patients with aortic valve disease. The epitome of frankness, Dr. Sears observed that only those findings supporting the conclusions of this paper would be presented.

Gastric secretion was studied by *Drs. E. M. Nanson and A. F. Bond* of Saskatoon by means of (a) a night secretion test, (b) a basal secretion test and (c) an augmented histamine test using four times the usual dose of histamine after an intramuscular injection of Phenergan, the three tests being carried out consecutively in each patient. The results were compared in patients with no peptic ulceration, patients with hiatus hernia without esophagitis, and patients with proven peptic ulcer. It was concluded that the augmented histamine test assesses the total secretory potential of the parietal cell mass of the stomach and that it adds little to the information yielded by the other two tests. While the night secretion test is probably the most useful, it is difficult to state that any one of these three tests is more valuable than the others, and they all have inherent limitations.

Cumulative survival was calculated by the life-table method in 120 male survivors of myocardial infarction by *Drs. J. A. Little, R. D. Roe and H. M. Shanoff* of Toronto. These patients, aged 30 to 80 years, were free of hypertension, secondary hypercholesterolemic states including diabetes and other complicating diseases. Total lipoproteins and standard S_f lipoproteins 0-12, 12-20, 20-100 and 100-400 were determined at the initial examination and annually thereafter. The results indicate that coronary heart disease is associated with high serum lipids but that once myocardial infarction has occurred, serum lipid concentration provides no information about future survival. This does not necessarily imply that attempts to lower serum lipids in an effort to prolong survival should not be undertaken, but it does imply that any value of this procedure remains to be proven.

Drs. P. Constantinides and R. N. Chakravarti of Vancouver described the production of advanced atherosclerosis with pearly plaques, exhibiting thick hyaline capsule, gruel and calcifications and considerable capillarization within the plaques, hemorrhage and necrosis in 62 rabbits by means of a "double lipemic exposure" technique. Agents causing (a) atheroma injury (Viosterol), (b) altered blood coagulation mechanisms (low dosage Russell Viper Thromboplastin) and (c) pressor and depressor hemodynamic effects (Adrenalin and Ecolid) were subsequently given to these severely atherosclerotic animals and to 48 normal rabbits. The results of these studies indicated that thrombosis can be elicited in the atherosclerotic aorta and coronaries of living rabbits by the synergism of systemically induced mural injury, blood coagulation and blood pressure change.

Platelets may die of old age (i.e. breakdown of internal economy), be consumed in coagulation and hemostasis (external economy), or succumb to both. *Drs. J. F. Mustard, E. A. Murphy and G. A. Robinson* of Toronto and the Ontario Veterinary College, Guelph, presented data indicating that the external platelet economy is important: (1) In atherosclerosis platelet survival is shorter, possibly because of endothelial damage and because the early stages of clotting are hyperactive. (2) Drugs which depress coagulation decrease platelet adhesiveness and prolong platelet survival. (3) Preliminary studies show that diet influences platelet survival. Sufficient dicoumarol restores platelet survival in atherosclerotic subjects to normal values but it is not known whether higher doses have any further effect and whether platelet survival in control subjects can be changed by dicoumarol. Preliminary studies of decay curves of isotopically labelled platelets in animals suggest that their destruction is attributable to the external economy.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

RAILWAYS AND TYPHOID

A matter that has been allowed to exist because people have grown used to it, and because no one has called attention to its danger, is the unsanitary method adopted by various railroad companies of disposing of excreta from the lavatories of their trains. The arrangement is crude, offensive, and a positive menace to public health. How dangerous it is, appears when it is recalled that such lavatories are often used by persons with various infectious diseases, such as the early stages of typhoid, where the excreta are a menace wherever they fall. If to those actually suffering from this sickness is added the unknown number of typhoid carriers, the danger becomes appreciable. And so with other disease. At present there is the possibility of cholera being carried into Canada. Let one or two undeveloped cases escape the port-examiner, and take train into the country, and an opportunity is at once given for the spread of this malady.—Excerpt from editorial, *Canadian Medical Association Journal*, 1: 261, March 1911.

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GENERAL PRACTICE

COLLEGE ASSEMBLY SPEAKERS

THE PRESIDENTS of medical organizations from three countries —Australia, the United States and Canada—will come to Vancouver, March 27 to 30, to address the fifth annual Scientific Assembly of the College of General Practice of Canada. Scientific speakers will also include a Professor of Medicine from Glasgow, the Dean of U.B.C.'s Medical School, the Director of Saskatchewan's Cancer Institute, and two Californians who respectively head the pediatrics and otolaryngology departments at their universities. These and a dozen other medical authorities will tailor their papers to the particular interest of general practitioners. General practitioners, whether they are members of the College or not, are urged to attend these sessions.

Professor Thomas Anderson, who heads the Department of Infectious Diseases at the University of Glasgow, will deliver the Canadian Tuberculosis Association Lecture at the College sessions on Monday morning. He will speak on "Virus in Respiratory Disease". A graduate of Glasgow University, Professor Anderson is a Fellow of both the Royal College of Physicians of Edinburgh and the Royal Faculty of Physicians and Surgeons of Glasgow. In the 1930's he did research work on chemotherapeutic agents and has lectured on infectious diseases at Glasgow University for two decades. In the past ten years, work at the Ruchill Hospital, including instruction of some 150 medical students annually, has involved much of his time. Professor Anderson will also participate in a symposium discussion on Monday afternoon. With Dr. W. M. Kirby, Professor of Medicine, University of Washington, and Dr. J. M. Adams, who heads the Pediatrics Department at the University of California, he will discuss the subject of influenza.

Dr. T. M. Greenaway

Professor Thomas Anderson

Dr. T. M. Greenaway of Sydney, Australia, is coming across the globe to deliver the "Medicine for Today" Lectures on the final two mornings of the Assembly. He will speak on "The Fat and the Thin" on Wednesday and on "Hypercholesterolemia" on Thursday. Dr. Greenaway will also participate in a symposium on Functional Dyspepsia on the Wednesday afternoon. President of the Royal Australian College of Physicians and an associate member of the College of General Practitioners of Australia, Dr. Greenaway is Lecturer in Clinical Medicine at the University of Sydney and Senior Physician at Royal Prince Alfred Hospital there. A native of Sydney, he was educated in that city and did postgraduate work both in London and in the United States. He is a Fellow of the Royal College of Physicians, London.

Dr. J. G. Walsh, president of the American Academy of General Practice, will address the Monday luncheon of the College Assembly. Dr. A. MacGregor Parsons, president of the Canadian Medical Association, will be the luncheon speaker on Wednesday.

Dean of the Faculty of Medicine, University of British Columbia, Dr. John F. McCreary will again be a speaker at the annual scientific sessions of the College of General Practice. He will talk on "The Role of the General Practitioner in Medical Education" because, he says, "I feel very strongly that it is very wrong for medical students to be exposed only to specialists in their undergraduate medical curriculum."

Another of the medical authorities contributing to this Assembly program is Dr. H. P. House of Los Angeles, who is head of the Department of Otolaryngology at the University of Southern California.

College officials are certain that family physicians will find the 1961 Assembly a particularly rewarding return for their trip to the West Coast. Vancouver medical men have planned hospitality and offer the Rocky Mountain grandeur as bonuses.

OBITUARIES

DR. GEORGES-GERARD ALLEYN, aged 47 years, died in Quebec January 30. A graduate of Laval University in 1941, he practised in Tadoussac, Quebec. Surviving are his widow, two sons and three daughters.

DR. ANDREW CAMERON BRADFORD, aged 56, died January 21 in Edmonton. After receiving his B.A. degree at the University of Alberta, he studied at McGill University where he received his M.D. in 1928. He practised in Maidstone, Sask., Vermilion, Alta., and in Edmonton.

Surviving are his widow and one daughter.

DR. DUNCAN A. CARMICHAEL, aged 76, died January 8 at Civic Hospital, Ottawa. After graduating from Queen's University in 1906, he studied in England and on his return practised in Peterborough and Oshawa. He served as superintendent of Riverglade Sanatorium in New Brunswick and as consultant surgeon for the Department of Veterans Affairs in Ottawa. He was medical superintendent of the Royal Ottawa Sanatorium.

Surviving Dr. Carmichael are his widow and one daughter.

DR. WILLIAM GEORGE KEYS, aged 48, of Weston, Ont., died January 1 in St. Michael's Hospital, Toronto.

Dr. Keys graduated from the University of Toronto in 1936 and had practised in Weston since then. He is survived by his mother, a brother and a sister.

DR. RENE LAPORTE, aged 71, died January 13 at his home in St. Lambert, Quebec. After graduating from the University of Montreal in 1913, he practised in Montreal.

Surviving are his widow, three sons and four daughters.

DR. PIERRE PERRIN, aged 77, died December 22 in Montreal. A graduate of Laval University in 1907, he practised in Montreal for 53 years.

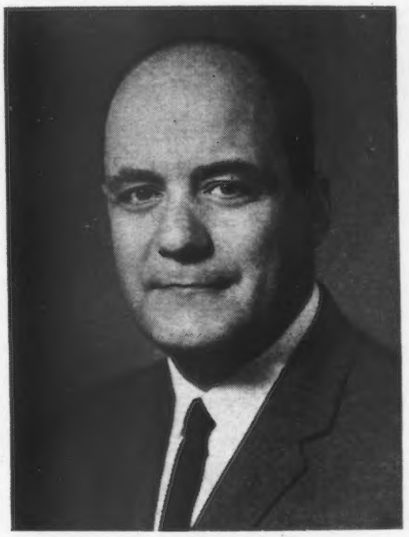
Surviving are his widow and a son.

DR. HENRI PINAULT, aged 62, died November 19 in Roberval where he had practised for 35 years. Dr. Pinault graduated from Laval University in 1923. Surviving are his widow, three sons, one of whom is Dr. Paul Pinault of Quebec, and one daughter.

DR. H. A. QUINTAL, aged 88, died January 5 in Montreal, Quebec. A graduate of the University of Montreal in 1895, Dr. Quintal is survived by two sons and four daughters.

DR. ROCK SAVARD, aged 31, died December 21 at Forestville, Quebec. A graduate of Laval University in 1956, he is survived by his parents, three brothers and three sisters.

DR. HEINZ LORD, 43, Secretary-General of the World Medical Association, died on February 4 in Chicago, where he was attending a meeting of the American Medical Association's annual congress on medical education and licensure. Dr. Lord had addressed the meeting on February 3 and suffered a heart attack later in the day. He died early the following morning.



Dr. Heinz Lord

Dr. Lord became Secretary-General of the World Medical Association last January, upon the retirement of Dr. Louis H. Bauer. A Peruvian citizen born in Germany, Dr. Lord was of German and Swiss descent. He was educated in Hamburg, Germany, and studied medicine at the Universities of Zurich, Berlin and Hamburg. He graduated from Hamburg University in 1942.

For his activity in a resistance movement he was arrested by the Gestapo and was confined in a concentration camp during most of World War II. Near the end of the war, he was on board a steamship containing 800 internees when it was bombed in the Baltic Sea. He was one of 28 survivors.

Returning to Hamburg after the war, he resumed his medical career at the Hamburg-Barmbek General Hospital and took specialist's degrees in surgery and urology. He moved to the U.S.A. in 1954 and took three additional years of surgical training at the Bridgeport, Conn., Hospital. In 1957 he received his licence to practise in the U.S.

Dr. Lord had taken an active part in medical organizational work at the local and international levels since 1949. He was a Fellow of the International College of Surgeons and a member of the American Medical Association, the Ohio Medical Society, and the county medical society at Barnesville, Ohio, where he was in private practice until his W.M.A. appointment.

Dr. Lord is survived by his widow, a son and a daughter.

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Residencies and Internships

PITTSFIELD AFFILIATED HOSPITALS (St. Luke's and Pittsfield General Hospitals) announce new program to include approved rotating internships; residencies in medicine, surgery, obstetrics and gynecology and pathology. Medical school affiliated. 450 beds available for teaching. Salary range, interns $250-$300, residents $325-$350. Applications for July 1, 1961, being reviewed. Apply to Director of Medical Education, Pittsfield Affiliated Hospitals, 379 East Street, Pittsfield, Massachusetts, U.S.A.

MEDICAL NEWS *in Brief*

AFFILIATION OF NATIONAL DEFENCE MEDICAL CENTRE WITH UNIVERSITY OF OTTAWA

An agreement by which the new National Defence Medical Centre in Ottawa is to become an affiliated hospital of the University of Ottawa and one of the university's teaching centres has been negotiated.

The new 350-bed Tri-Services Hospital, located at 355 Smyth Road in the Alta Vista district, was built by the Department of National Defence at a cost of nearly $8,000,000. It is expected to be ready next May for installation of about $2,000,000 worth of equipment and furnishings. It then will replace the Rockcliffe Military Hospital and the Veterans' Pavilion at the Ottawa Civic Hospital. It brings to almost 2750 the number of teaching beds at the University's disposal in the Ottawa area.

The agreement was signed by Very Rev. Henri F. Légaré, O.M.I., Rector, and Dr. Jean-Jacques Lussier, Dean of Medicine, for the University, and Rear-Admiral T. B. McLean, Surgeon-General of the Canadian Forces, and Air Commodore A. A. G. Corbet, Deputy Surgeon-General, for National Defence, recently retired.

The hospital is to be in operation next July and will thus be available to the medical faculty at the beginning of the 1961-62 academic year.

The Department of National Defence and the University of Ottawa will jointly facilitate medical research activities and collaborate in establishing and implementing a medical graduate training program at the hospital, whose scientific and professional military staff engaged in teaching are to receive University appointments. The appointments are to be made by the University on the recommendation of the Joint Committee on Hospital-University Relations. This 12-member committee will also have certain other powers under the agreement. The University's committee members are Dr. Jean-Jacques Lussier; Dr. Joseph Auer, Assistant Dean; Dr. Antony Fidler, chairman of Medicine; Dr. J. B. Ewing, acting chairman of Surgery; a third department chairman and one member of the administrative council, both to be named. National Defence members are Rear-Admiral McLean; Group Capt. H. J. Bright, commanding officer of the new hospital; Air Commodore A. A. G. Corbet; a representative of the Department of Veterans Affairs, and the hospital's chiefs of medicine and surgery.

The Department's approval will be necessary for the appointment of civilian consultants by the University for the hospital, but the medical faculty will establish the curriculum. While in the hospital the undergraduate students will be under that institution's administrative officer for disciplinary purposes.

Nat. Def. Photograph, Canada

Air Commodore A. A. G. Corbet signs the agreement in the presence of (left to right) Very Rev. Henri F. Légaré, O.M.I., Rear-Admiral T. B. McLean and Dr. Jean-Jacques Lussier.

PROPOSED EDUCATION PROGRAM IN U.S. FOR FOREIGN PHYSICIANS

The American Medical Association, in a recent statement of policy, required that graduates of foreign medical schools should meet the same minimum standards of education as graduates of U.S. medical schools, as nearly as can

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be measured. At the last examination of the Educational Council for Foreign Medical Graduates (E.C.F.M.G.) in September, more than 70% of the foreign physicians passed. The total represented 5306 of 7308. As well, 1405 foreign doctors took the test in 66 centres outside the United States and 962 passed.

An immediate problem then arose in regard to the group of 2481 foreign doctors who failed their examinations and faced deportation; and in regard to hospitals, after December 31, since they will face loss of approval of their intern and residency programs if the programs include medical graduates who are not certified by E.C.F.M.G.

A solution seems to have been arrived at with the statement of Dr. Lelond S. McKittrich, Boston, chairman of the A.M.A. Council on Medical Education and Hospitals, that through mutual agreement with the State Department in Washington, the American Medical Association, the American Hospital Association, and the Association of American Medical Colleges, hospitals will be urged to develop a special education program for this group of foreign graduates who failed, but one not involving patient care. The proposal calls for the program to be carried out until June 30, 1961. This will permit the U.S. Immigration and Naturalization Service to extend the educational visas of these foreign doctors and enable them to take the examination next April 4.

Details of the educational program will be worked out by each hospital in order to conform to the specific educational needs of the foreign doctors. Under such a proposal there will be no sudden forced exodus of those who have failed previous examinations. Hereafter, foreign doctors who seek training as interns and residents in the United States under the exchange program must pass examinations in their own countries before going to the U.S. Only then will they be allowed to apply for a five-year exchange-visitor visa.

WORLDWIDE RESEARCH IN MENTAL ILLNESS

A World Health Organization Expert Committee on Mental Health, which held a recent session in Geneva, observed that research on an international as well as a national scale is necessary if further advances are to be made in preventing mental illness. The Committee defined areas of priority for mental health research, placing high on the list researches into brain function, social attitudes, effect of cultural change, psychoses of the aged, effects of nutrition and genetic factors. In its opinion the administration of mental health programs should also be studied.

It was suggested that research was needed on the kinds of stresses to which high policy makers and top administrators are subjected. It was observed that although the importance of leadership is repeatedly stressed, we know little about the human elements that

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Editorial,
Canadian Medical Association Journal
83:822, October 8, 1960

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Arnold Branch, M.D., K. C. Rodger, M.D.,
R. W. Lee, M.D., and Edna E. Power, B.A.

Canadian Medical Association Journal
83:991-996 Nov. 5, 1960

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characterize the leader. It was suggested that the stresses in high position are too great for normal people, and consequently people with psychopathic makeup often become leaders. Studies in different cultures might perform a useful function by promoting knowledge of what is required for leadership roles.

Another important field for research, the Committee agreed, was that presented by the mental problems of ageing and the aged, since in many countries of the world the proportion of old people in the population is increasing. Knowledge is required concerning the physical, social and psychological factors in ageing which contribute to mental problems. The effects on health of factors such as work, housing, nutrition and a sense of being needed, merit investigation.

Although one of the major achievements of psychiatry has been to elucidate the effect of one serious deficiency disease, pellagra, on the nervous system, surprisingly little research has been done on the relationship between nutrition and mental illness in general. Psychological symptoms sometimes are an important feature of protein deficiency in children, and it is also known that some forms of "alcoholic psychosis" are due to nutritional deficiencies. Nutritional failure has even been suggested as an explanation of alcoholism.

Genetic studies were considered by the Committee to present another fruitful line of investigation. For example, it has recently been discovered that mongoloid children possess an extra chromosome. While recognizing the difficulty of separating genetic and environmental factors, the Committee believed that such analyses should be undertaken.

The size of mental hospitals also was considered, and it was thought that experiment and research were still needed to find out what type of hospital best fits the needs of patients with various kinds of mental disorders: acute, chronic, recurrent, in persons of different ages, with different symptoms, and in different parts of the world.

The spread of rumour, anxiety and even panic can be observed in groups, and as an emotion spreads it gains force. The Committee agreed that a first step in determining the means of transmitting feelings, either of a person or a group, was a study of non-verbal communications and cues received below the level of awareness.

The Committee believe that the research function of an international organization such as WHO is not to duplicate national effort but rather to encourage, sponsor and co-ordinate research work and to undertake tasks that particularly require an international approach.

SURVEY OF MANPOWER IN THE HEALTH SCIENCES FIELD

The current availability of health scientists and forecasts of future requirements for such personnel are being studied in a survey of the nation's health science man-

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power needs by a Federation of American Societies for Experimental Biology. These matters have a direct relationship to the future of American public health, medicine, dentistry, veterinary medicine and industry.

The survey has been undertaken because of the underlying need for more personnel in the health sciences. Objectives of the survey will include: (1) an assessment of the present supply and demand for scientists in each of about 12 basic health fields; (2) projections of such supply and demand for the next 10 to 20 years; and (3) recommendations as to how the increased demand for these scientists may be met.

Dr. John T. Cowles, director of educational planning for the health professions at the University of Pittsburgh, is director of the project. Dr. Lowell S. Levin has joined Dr. Cowles' staff in Pittsburgh to serve as full-time associate director of this survey.

Members of the guidance committee for the over-all project are: Dr. E. B. Fred, University of Wisconsin (chairman); Dr. K. K. Chen, Lilly Research Laboratories; Dr. Philip Handler, Duke University School of Medicine; Dr. John S. Nicholas, Yale University; Dr. Orr E. Reynolds, Office of Science, Department of Defense; Dr. W. H. Sebrell, Jr., Columbia University School of Public Health; Dr. Maurice B. Visscher, The University of Minnesota School of Medicine; Dr. Herbert E. Longenecker, Tulane University; and Dr. Cyrus C. Erickson and Dr. Milton O. Lee, both of the Federation of American Societies for Experimental Biology.

A planning phase, which should be completed by June 1961, will focus at first on the review of manpower problems in microbiology. The advisory panel on microbiology includes: Dr. Gail M. Dack, University of Chicago (Chairman); Dr. Howard Gest, Washington University; Dr. Edwin H. Lennette, California Department of Public Health; Dr. Roger D. Reid, Office of Naval Research; Dr. John C. Sylvester, Abbott Laboratories, Chicago; Dr. Ned B. Williams, University of Pennsyl-

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vania, and Dr. George A. Young, Jr., University of Nebraska.

Some of the data being sought include: number of persons now employed, salary levels, space requirements, current student enrolments, research expenditures, training program income, instructional costs and student aid.

The over-all project, which will require three to five years to complete, will be expanded from microbiology to include most, if not all, of the health science fields.

The pilot phase of the project is being supported by an $87,000 grant from the National Institutes of Health. The University of Pittsburgh has been selected as the project site because of its available personnel resources and electronic computer facilities which will be required for the survey.

Further information may be obtained from Dr. John T. Cowles, University of Pittsburgh.

MORTALITY AND LONGEVITY STATISTICS FOR THE ELDERLY

America's senior citizens have shared substantially in the marked reductions in mortality during recent decades, according to statistics of the Metropolitan Life Insurance Company, although striking reductions in mortality among children and young adults have tended to obscure the progress at the older ages. However, a comparison of 1958's mortality rates at ages 60 and over with those of the 1929-31 period show marked reductions.

Among white men, a reduction was recorded at each age from 60 to 80 years, the decrease averaging about 13%. For example, at age 60 the death rate fell from 26.4 per 1000 to 22.6 in 1958, and at age 75 the rate dropped from 85.3 to 73.3 per 1000. Women have made considerably greater gains than men, the reductions ranging from as much as 47% at age 60 to more than 30% up to age 80.

Reductions in mortality have been accompanied by increases in longevity for older persons. In 1958 women at age 60 had an expectation of life of 19.2 years, a gain of 3.1 years since 1929-31. At age 80, the remaining lifetime averaged 6.4 years in 1958, a gain of 0.8 years. For men, the age 60 figure was 15.7 years in 1958, a gain of one year; and at age 80 life expectancy was 5.8, a gain of half a year.

A reflection of the improvement in mortality and longevity is seen in the increased chances of older people to survive an additional 10 years. For those currently reaching age 65, the chances of living at least another 10 years are almost 3 in 5 for men and 3 in 4 for women. Even at age 75, the chances of survival for 10 years are almost 1 in 3 for men and more than 2 in 5 for women.

The Metropolitan statisticians concluded that the improved record of longevity at the older ages reflects the remarkable advances in medicine and public health and their widespread application, the expansion of hospital facilities and services, better nutrition, fuller knowledge of personal hygiene, and the general rise in living standards. — Metropolitan Information Service.